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### Title

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### Permalink

<https://escholarship.org/uc/item/4dh9w8ch>

### Journal

The American Journal of the Medical Sciences, 364(3)

### ISSN

0002-9629

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### Publication Date

2022-09-01

### DOI

10.1016/j.amjms.2022.04.015

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# Implications of microvascular dysfunction and nitric oxide mediated inflammation in severe COVID-19 infection

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## ABSTRACT

Infection with COVID-19 has resulted in over 276,000 deaths in the United States and over 1.5 million deaths globally, with upwards of 15% of patients requiring hospitalization. Severe COVID-19 infection is, in essence, a *microvascular disease*. This contention has been emphasized throughout the course of the pandemic, particularly due to the clinical manifestation of severe infection. In fact, it has been hypothesized and shown in particular instances that microvascular function is a significant prognosticator for morbidity and mortality. Initially thought to be isolated to the pulmonary system and resulting in ARDS, patients with COVID-19 have been observed to have acute cardiac, renal, and thrombotic complications. Therefore, severe COVID-19 is a vascular disease that has systemic implications. The objective of this review is to provide a mechanistic background for the microvascular nature of severe COVID-19 infection, with a particular emphasis on dysfunction of the endothelial glycocalyx and nitric oxide mediated pathogenesis.

**Keywords:** COVID-19; Microcirculation; Endothelial glycocalyx; Cardiovascular disease; Nitric oxide. [Am J Med Sci 2022; ■(■):1–6.]

## INTRODUCTION

Infection with COVID-19 has resulted in over 276,000 deaths in the United States and over 1.5 million deaths globally, with upwards of 15% of patients requiring hospitalization.<sup>1</sup> The majority of patients with COVID-19 experience upper respiratory symptoms, weakness, and fatigue, with anosmia and dysgeusia reported in some instances.<sup>2,3</sup> Moderate (i.e., requiring hospitalization) and severe (i.e., requiring intensive care unit (ICU) level of care – ventilation and/or pressors) manifestations of COVID-19 include acute respiratory distress syndrome (ARDS) and new incident heart failure.<sup>2</sup> Interestingly, the pediatric manifestation of severe COVID-19, known as pediatric multisystem inflammatory syndrome (PMIS), shares features with Kawasaki disease, a medium-vessel vasculitis observed in children, and Kawasaki shock syndrome, highlighted by coronary microvascular dysfunction.<sup>4,5</sup> The clearly dichotomous presentation of severe disease in adult and pediatric populations highlights the interesting biological role of the microvasculature in COVID-19.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), the etiologic agent of COVID-19, invades host cells via the ACE2 receptor by binding of viral surface spike (S) protein, suggestive of the role of endothelial dysfunction in disease manifestation.<sup>6,7</sup> Thus,

essential to the pathogenesis of severe COVID-19 is microvascular dysfunction, systemic inflammation, and cytokine storm.<sup>8,9</sup> At its etiologic root, COVID-19 triggers endothelial exocytosis, which results in microvascular thrombosis and inflammation.<sup>10</sup> In fact, laboratory findings of patients with severe COVID-19 are consistent with hypercoagulability, hallmarked by elevated D-Dimer, von Willebrand Factor (VWF), and Factor VIII, clinically identified as “COVID-Coagulopathy”.<sup>11</sup> The contention that severe COVID-19 infection is a disease of the microcirculation has been emphasized throughout the course of the pandemic, particularly due to the clinical manifestation of severe infection. In fact, it has been hypothesized and shown in particular instances that microvascular function is a significant prognosticator for morbidity and mortality.<sup>12,13</sup>

More recently, the role of nitric oxide signaling<sup>14</sup> and dysfunction of the endothelial glycocalyx<sup>15</sup> has come to the forefront of the discussion of the microvascular pathogenesis of COVID-19. The objective of this review is to provide mechanistic background for the microvascular nature of severe COVID-19 infection, with a particular emphasis on these components. We will begin by introducing the microvascular manifestations of COVID-19 clinically in both adults and pediatric patient populations, with a particular emphasis on cardiovascular disease. Unique to our analysis is a

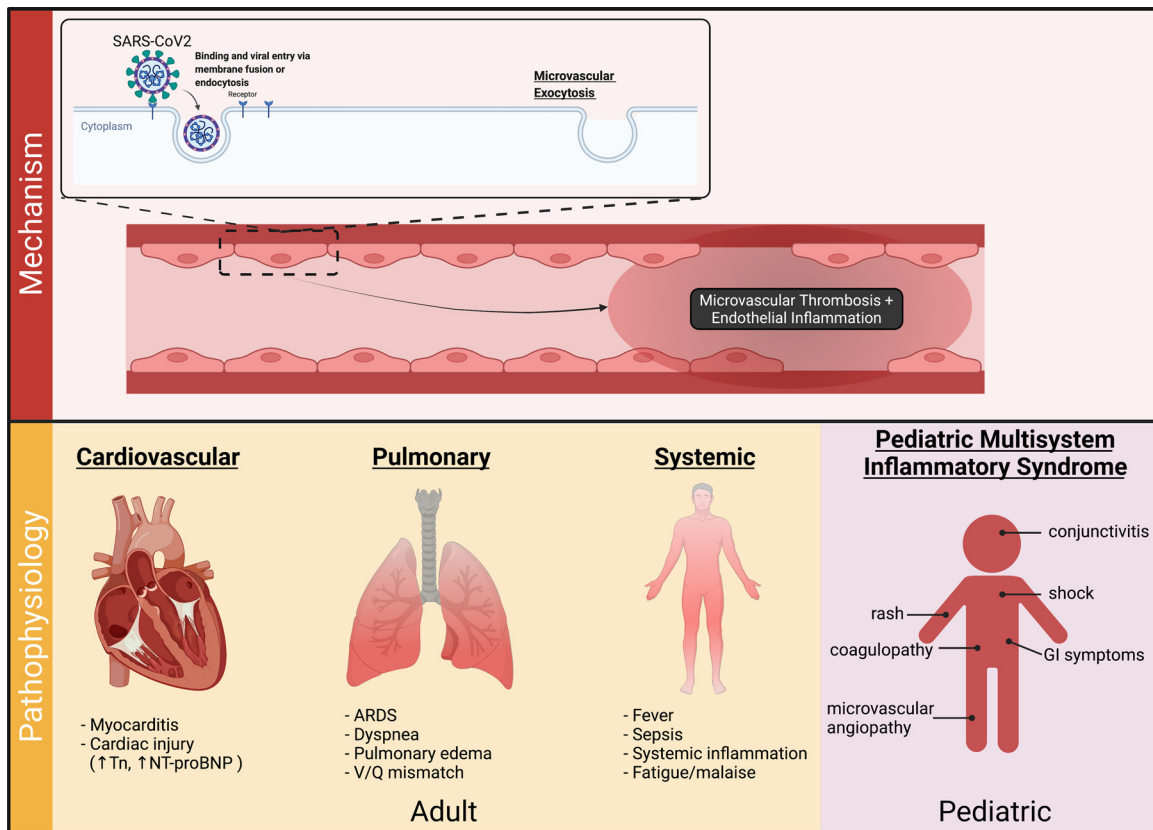


FIGURE 1.

comparison of differences in the clinical manifestation of microvascular dysfunction in adult and pediatric populations. Next, we provide a discussion of the pathophysiologic and molecular basis for microvascular dysfunction in COVID-19, discussing the role of endothelial glycocalyx injury as well as the role of nitric oxide in propagating systemic inflammation. We conclude by discussing potential interventions related to nitric oxide in COVID-19, with a brief discussion on the potential of nitric oxide releasing nanoparticles for combatting systemic inflammation (Figure 1).

### Clinical manifestations of microvascular dysfunction in COVID-19

The clinical manifestation of severe COVID-19 results from systemic inflammation and thrombosis. Mechanistically, COVID-19 is known to trigger endothelial cell exocytosis, which drives microvascular inflammation and thrombosis.<sup>10,11</sup> Subsequently, microvascular thrombosis drives the clinical phenotype of severe COVID-19 in the ICU, namely venous thromboembolism (VTE) and deep vein thrombosis (DVT) and related complications.<sup>16,17</sup> Serum inflammatory markers in severe COVID-19, including elevated C-reactive protein, interleukin 6 (IL-6), increased fibrinogen, and elevated erythrocyte sedimentation rate (ESR), are consistent with cytokine storm, further highlighting the role of systemic inflammation in disease pathogenesis.<sup>18</sup> These clinical observations highly suggest

that microvascular inflammation is the primary mediator of systemic inflammation in these patients.

COVID-19 is, in its essence, a microvascular disease, in which direct infection by the SARS-CoV2 virus triggers endothelial injury resulting in endothelial exocytosis.<sup>19</sup> Endothelial exocytosis directly results in microvascular thrombosis and microvascular inflammation, which in turn progress into systemic thrombosis and inflammation.<sup>16,17</sup> During exocytosis, endothelial cells release VWF and P-selectin from granules, known as Weibel-Palade bodies. P-selectin interacts with VWF, which is one mechanism of COVID-19 related thrombosis. There are three primary mechanisms of viral mediated endothelial exocytosis:

1. Viral attachment to receptors on endothelial cells, including ACE2-R (Angiotensin-Converting Enzyme 2-Receptor)
2. Indirect activation of exocytosis
3. Direct infection of endothelial cells with viral peptides

Recent studies have identified that in the context of systemic SARS-CoV2 infection, viral attachment and entry via the ACE2-R is the primary mechanism of viral mediated exocytosis.<sup>10,20</sup> These studies have only further cemented the idea that COVID-19 initiates a cycle of microvascular dysfunction followed by endothelial

exocytosis, which triggers systemic thrombosis and inflammation.<sup>9</sup>

Patients with comorbid cardiovascular disease (CVD) are at a uniquely increased risk of severe COVID-19 infection, which requires ICU hospitalization and results in high short-term mortality.<sup>21,22</sup> The mechanism underlying this association is unclear, though arterial and venous thrombosis and vascular inflammation are likely mediators. Furthermore, the SARS-CoV2 virus itself can cause myocarditis and myocardial injury by an unknown mechanism; however, it has been suggested that SARS-CoV2 is able to infect endothelium within the myocardium and even cardiomyocytes.<sup>20,23</sup> The suggested mechanism involves the presence of ACE2-R on both endothelium and cardiomyocytes, though direct infection in cardiomyocytes has only been demonstrated in induced pluripotent stem cells.<sup>24</sup> Clinical evidence of myocardial injury includes subclinical elevation of high sensitivity troponins, which have been associated with increased mortality in COVID-19 patients,<sup>25</sup> and subclinical elevation of N-terminal pro brain natriuretic peptide (NT-proBNP).<sup>26</sup> Whether elevated troponins and NT-proBNP result from direct myocardial injury or myocardial injury secondary to endothelial disruption and impaired microvascular compliance is unknown.<sup>27</sup> Recently, however, the MYSTIC study of microvascular dysfunction in COVID-19 found, in a small cohort, that indices of endothelial dysfunction, namely ADAMTS-13, a VWF protease, and VEGF-A, better predicted mortality compared with indices of myocardial injury.<sup>13</sup> In fact, ADAMTS-13 inversely correlated with COVID-19 severity. These data suggest that the pathogenesis of severe COVID-19 is rooted in microvascular dysfunction. Taken together, there exists a dichotomy in the presentation of cardiovascular complications secondary to COVID-19 infection involving both direct myocardial injury and endothelial dysfunction (**Figure 1**).

Contrasted with adults, the manifestation of COVID-19 in pediatrics, though rare, is known as the pediatric multisystem inflammatory syndrome (PMIS), which shares numerous features with Kawasaki Disease.<sup>4,5</sup> Symptoms of PMIS are diverse and have included rash or conjunctivitis, hypotension or shock, myocardial dysfunction, coagulopathy, or gastrointestinal symptoms, and elevated markers of inflammation. Furthermore, PMIS is associated with a systemic cytokine storm and inflammatory shock and is known to behave as a microvascular angiopathy. Whether PMIS is associated with myocardial perfusion defects secondary to coronary microvascular dysfunction is unknown and is an area of future research.

### The pathophysiology of microvascular dysfunction in COVID-19 and ARDS

COVID-19 is a microvascular disease that has systemic implications beyond the pulmonary system and ARDS. At the root of the ARDS and organ failure seen in

COVID-19 are endothelial dysfunction and vascular leak. Studies of the assessment of microvascular hemodynamics *in vivo* in COVID-19 have provided insight into its pathophysiology. In the MYSTIC study, up to a 90% decrease in capillary (4–6  $\mu\text{m}$ ) density and a reduction of red blood cell velocity was observed in sublingual microscopy of COVID-19 patients.<sup>13</sup> Furthermore, vascular densities of vessels with 4–10  $\mu\text{m}$  in COVID-19 patients with and without ventilation were shown to decrease compared to the control group. However, no such difference was observed for vessels > 10  $\mu\text{m}$ , suggesting microvascular dysfunction in COVID-19 is restricted to capillaries.<sup>13</sup> Of note, in this same study, perfused boundary region (PBR), an index of glycocalyx injury,<sup>28</sup> was elevated in COVID-19 patients regardless of mechanical ventilation, though more dramatically elevated in patients requiring mechanical ventilation.<sup>13</sup> COVID-19 is also thought to increase glycocalyx permeability and mediate glycocalyx thinning, with levels of hyaluronic acid and syndecan-1 correlating with need for ventilation.<sup>13,29</sup> Taken together, these results suggest that dysfunction of the endothelial glycocalyx independently associates with disease severity.

Severe COVID-19 infection is hallmarked by changes in microvascular hemodynamics, oxygenation, angiogenesis, and thrombogenesis. Indices of microvascular function, namely ADAMTS13, VEGF-A, PBR, and Angpt-2, better predicted mortality in COVID-19 over a 60-day hospitalization compared with classic indices of myocardial injury and inflammation.<sup>13</sup> Furthermore, capillary loss seen via sublingual microscopy correlated with oxygenation levels, SOFA, and SIC scores, further demonstrating the value of microvascular function in assessing COVID-19 patients.<sup>13</sup> Postmortem analysis of pulmonary capillaries in COVID-19 demonstrated capillary plugging from fibrous microthrombi, suggesting systemic thrombosis is a primary mechanism of pulmonary COVID-19 infection.<sup>10,30</sup> An increase in Angpt-2 in COVID-19 patients especially those on mechanical ventilation suggests that Angpt-2 mediated endothelial leak is a predominant effect of COVID-19 on the microcirculation.<sup>31,32</sup> In this same study, dysregulated angiogenesis, indicated by an increase in VEGF-A and sFLT1, further demonstrated that COVID-19 results in microvascular dysfunction. Thus, it is clear that COVID-19 infection results in significant changes in microvascular hemodynamics and angiogenesis, further supporting the hypothesis that severe COVID-19 infection is truly a disease of the microcirculation.

Given the microvascular nature of severe COVID-19 infection, there has been much interest in nitric oxide-based therapies to limit viral load within the lungs to prevent and treat ARDS and acute lung injury. Prior to discussing the role of nitric oxide (NO) in severe COVID-19 and ARDS, we will first provide a brief overview of microvascular dysfunction in ARDS. The mechanism of ARDS secondary to pulmonary infection involves a hypothesized loss of surfactant,

resulting in end-expiratory alveolar collapse and reduction in lung compliance. Histologically, ARDS is defined by three phases: (1) acute phase, or diffuse alveolar damage (DAD), which includes alveolar edema, hyaline membranes, and thickened alveolar septae, (2) proliferative phase, and (3) fibrotic phase. From Starling forces, this results in increased fluid conductance and pulmonary edema, which is not pressure driven, contrary to cardiogenic pulmonary edema. Alveolar edema in ARDS results in ventilation/perfusion (V/Q) mismatch and subsequent hypoxemia. Treatment involves oxygen to maintain arterial oxygen saturation and positive end-expiratory pressure (PEEP) to increase pulmonary compliance. In the context of COVID-19 infection, attachment to respiratory epithelium by the ACE2-R is thought to be the primary cause for ARDS secondary to inflammation and cytokine storm (**Figure 1**).

NO is critical in the pathogenesis of ARDS, particularly with regard to systemic hypoxemia and endothelial dysfunction, independent of impaired alveolar oxygen diffusion and endothelial exocytosis. In particular, a decreased nitric oxide/reactive oxidation species (NO/ROS) ratio is known to result in M1 macrophage activation and erythrocyte membrane damage.<sup>33,34</sup> Hemoglobin released from damaged erythrocytes scavenges endothelial NO and contributes to oxidative stress, hypoxia, and endothelial dysfunction.<sup>35-37</sup> NO mediated transformation of M1 macrophages to M2 macrophages may be useful in preventing this cascade in the context of acute lung injury and ARDS in severe COVID-19 infection. Furthermore, when ARDS is present, NO has been shown to improve arterial oxygenation by improving V/Q mismatch independent of PEEP.<sup>38,39</sup> As elderly patients, patients with cardiovascular disease, and patients with microvascular complications from diabetes are known to have decreased endogenous NO production and are known to more likely have severe COVID-19 infection, supplementation with NO may help in improving mortality and reducing hospitalization in these susceptible populations.<sup>40,41</sup> Thus, the critical nature of NO in systemic endothelial dysfunction and hypoxemia makes it an attractive target for treatment of severe COVID-19 infection.

### Nitric oxide based therapies in COVID-19

Most NO based therapies are still under development and have recently increased in prevalence and testing particularly due to their potential ability to help reduce mortality in severe COVID-19 infection and ARDS. Currently, there are two primary mechanisms for NO delivery that have been developed: (1) inhaled NO and (2) NO releasing nanoparticles. In prior studies, inhaled NO was not shown to reduce mortality in ARDS.<sup>42,43</sup> This is likely due to decreased bioavailability secondary to increased alveolar septae thickness and DAD observed in ARDS. Within the COVID-19 pandemic, two inhalation NO therapies, Bellerophon Therapeutics INOpulse<sup>14</sup> and VERO

Biotech's GENOSYL DS<sup>®</sup> inhaled NO<sup>44</sup> have been evaluated for severe infection. While one study<sup>44</sup> has demonstrated improvement in symptoms in outpatient COVID-19, whether these therapeutics have an influence on mortality in severe COVID-19 is yet to be seen. NO releasing nanoparticles have shown much promise for limiting inflammation, preventing ischemia reperfusion, and more recently, has demonstrated improved microvascular perfusion in an animal model of sepsis.<sup>45-47</sup> However, to date, no trials have been performed with NO releasing nanoparticles. In summary, despite the promise of NO based therapies for combatting systemic inflammation and sepsis, particularly in COVID-19, further translational development is required before assessing clinical impact.

### SUMMARY

In severe COVID-19, microvascular function is a significant prognosticator for morbidity and mortality. Initially thought to be isolated to the pulmonary system and result in ARDS, patients with COVID-19 have been observed to have acute cardiac, renal, and thrombotic complications. Sequelae from systemic thrombosis, namely stroke and pulmonary embolism, have also been reported. Therefore, severe COVID-19 is a vascular disease that has systemic implications. Due to the vascular nature of severe COVID-19, its effect on the microcirculation has been of great interest. Clinical manifestations of severe COVID-19 include systemic inflammation and coagulopathy, namely venous thromboembolism and deep vein thrombosis. Moreover, the clinical manifestations of severe COVID-19 may differ in adult and pediatric populations. Consistent with this observation is the manifestation of pediatric multisystem inflammatory syndrome (PMIS), which shares many features with Kawasaki syndrome. Importantly, functional capillary densities were shown to decrease upon infection with COVID-19, suggesting changes in microvascular hemodynamics consistent with COVID-19 being a microvascular disease. Mechanistically, the microvascular nature of severe COVID-19 infection described here emphasized endothelial exocytosis, endothelial glycocalyx dysfunction, and nitric oxide mediated pathogenesis focusing on the role of nitric oxide signaling in ARDS. Severe COVID-19 was shown to increase glycocalyx thinning and permeability. Furthermore, RBC injury in COVID-19 results in hemoglobin mediated nitric oxide scavenging which may result in hypoxia, endothelial dysfunction, and oxidative stress. Particularly in COVID-19 induced ARDS, NO based therapy may improve arterial oxygenation independent of ventilation. Potential interventions related to nitric oxide, specifically nitric oxide releasing nanoparticles, in COVID-19 may be therapeutic in treating severe infection.

### CONCLUSIONS

Severe COVID-19 is a systemic disease of the microcirculation. Despite much of the work into the

microvascular effects of COVID-19, many open questions still remain. For instance, with respect to cardiovascular injury, whether elevated troponins and NT-proBNP result from direct myocardial injury or myocardial injury secondary to endothelial disruption and impaired microvascular compliance is unknown. Furthermore, the pathophysiology of PMIS in children is unclear, with few management options. Management of severe COVID-19 remains limited to ventilatory support and pressors. NO based therapies have shown much promise, though future development is required before clinical implementation. In summary, the COVID-19 pandemic has paved the way for advancements in NO based and microcirculation specific therapies, with significant translational advances still required prior to clinical impact.

## DECLARATION OF COMPETING INTEREST

There are no potential conflict of interest, real or perceived, by the authors.

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Submitted January 26, 2021; accepted April 14, 2022.

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