Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Microvascular disease confers additional risk to COVID-19 infection

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ABSTRACT

The majority of fatalities thus far in the COVID-19 pandemic have been attributed to pneumonia. As expected, the fatality rate reported in China is higher in people with chronic pulmonary disease (6.3%) and those who have cancer (5.6%). According to the American College of Cardiology Clinical Bulletin "COVID-19 Clinical Guidance for the CV Care Team", there is a significantly higher fatality rate in people who are elderly (8.0% 70–79 years; 14.8% ≥80 years), diabetic (7.3%), hypertensive (6.0%), or have known cardiovascular disease (CVD) (10.5%). We propose a biological reason for the higher mortality risk in these populations that is apparent. We further present a set of pathophysiological reasons for the heightened danger that could lead to therapies for enhanced management and prevention.

Background

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-Cov2) results in COVID-19 which can lead to severe illness and death. The majority of fatalities are due to pneumonia. The overall mortality risk reported on March 28, 2020 varies from 2.3% in China, 2.7% in Iran, and 0.5% in South Korea. As expected, the fatality rate reported in China is higher in people with chronic pulmonary disease (6.3%) and those who have cancer (5.6%). According to the American College of Cardiology Clinical Bulletin "COVID-19 Clinical Guidance for the CV Care Team", there is a significantly higher fatality rate in people who are elder (8.0% 70–79 years; 14.8% ≥80 years), diabetic (7.3%), hypertensive (6.0%), or have known cardiovascular disease (CVD) (10.5%) [1]. The reason for the higher mortality risk in these populations is not apparent. Defining the pathophysiological reasons for the heightened danger could lead to therapies for enhanced management and prevention.

Inhalation of COVID-19 onto airway epithelial cells triggers the earliest defense of the viral invasion, which is the innate immune system [2]. This initial immune response is triggered by cellular danger signals such as interleukins that in turn initiate a movement of white cells to the sites of infection. COVID-19 is no exception. Recent evidence shows that robust proinflammatory cytokines are produced in response to upper and lower respiratory COVID-19 infection [3]. The initiation of innate mechanisms plays a significant role in the development of efficacious adaptive immunity. Failure on this front line can lead to an ineffective adaptive immune response. Adaptive immunity plays a critical role in eliminating the pathogens during the late phase of infection [4]. Failure or over exuberance of the innate immune response increases the risk of a severe or even fatal outcome.

Individuals who are older, diabetic, hypertensive, or have known CVD may have a common underlying health issue that impairs innate immunity. This paper will explore the hypothesis that these patients are disadvantaged for a vigorous innate immune response due to underlying microvascular disease. If the hypothesis is proven, it could provide insights into additional therapies and management to reduce the higher mortality risk in this population.

Hypothesis: Microvascular disease increases the risk from COVID-19

Microvascular disease (MVD) is fundamentally unhealthy small arteries, such as arterioles and capillaries. These small vessels perfuse the tissue in organs. MVD is receiving considerable attention due to its high prevalence and impact on clinical outcomes. Research demonstrates that the extent of atherosclerosis is directly related to the extent of microvascular disease. This relationship is unrelated to the degree of stenosis in larger arteries. Therefore, someone with substantial subclinical atherosclerosis may have considerable MVD [5–7]. A common denominator of the elderly, diabetic, or hypertensive patient is the frequent presence of atherosclerosis; clinical or subclinical. The probability is high that the patients with higher mortality rates from COVID-

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19 have MVD.

Neutrophils perform a significant function in the innate immune response. Their first task is to travel to contaminated tissue. This migration occurs through the arterial system. Neutrophils reaching the infected tissue release the enzyme myeloperoxidase (MPO) from azurophilic granules. MPO then combines with hydrogen peroxidase (H_2O_2) to create hypochlorous acid (HOCl). This substance is viricidal, and its formation is a crucial step in innate immunity [8]. Recent evidence from COVID-19 infected patients demonstrated that in severe disease the levels of neutrophils was significantly elevated as compared to patients who had mild disease [9]. This observation can be accounted for in patients with COVID-19 by the excessive production of proinflammatory cytokines such as interleukin-6 (IL-6) which has been shown to regulate neutrophils to the site of infection and inflammation [10].

MVD in the lung impedes the process of HOCl production from neutrophils in several ways. First, MVD reduces tissue perfusion of the lung. This reduction in blood flow will decrease how many neutrophils extravasate into the diseased tissue. Second, microvascular endothelial cells produce H_2O_2. This is the predominant substance driving vasodilation of the small arteries. Occlusive MVD leads to a reduced amount and dysfunction of the endothelial cells [11]. Therefore, there is less H_2O_2 available to interact with MPO to generate the antiviral HOCl. The consequence of MVD hampering the innate immune response leads to greater risk of a severe or life-threatening infection.

With this hypothesis, some of the MPO released would not have H_2O_2 with which to combine. In addition, higher levels of neutrophils would generate more MPO. This may lead to higher MPO serum concentrations. MPO is a known independent predictor of increased myocardial infarction risk [12]. Acute cardiac injury and myocardial infarction are reportedly higher in the COVID-19 high mortality risk population. Some of that elevated risk might also be due to increased cardiometabolic demand in an environment of coronary MVD [13]. This would increase the risk for a myocardial infarction. It is being reported that heart attack risk is elevated in these seriously ill patients. Elevated systemic MPO levels may be a significant contributor for the increased CV risk being observed.

This hypothesis is compatible with the observation in the United States that children are at a lower risk of COVID-19 complications while early observations show heightened risk in people 40 to 69 years of age. This country has a high incidence of obesity and CVD in younger people [20,21,14]. With this hypothesis, it is possible to conjuncture that the statistics for age and severe COVID-19 infections in the USA will trend to a younger age group.

Testing the hypothesis

Several testing opportunities are available for this hypothesis. One way is the measurement of serum MPO levels. Patients destined to life-threatening infection would be expected to have higher MPO than those with milder illness. Examination of infected lung tissue is another way to test the hypothesis. One analysis is to compare quantitative measures of MPO, H_2O_2, and HOCl in COVID-19 survivors and non-survivors. Another examination is to estimate the degree of MVD in deceased patients to survivors. Age matched survivors could have noninvasive vasomotor testing for MVD [15]. It is possible to assess the merit of the hypothesis expeditiously.

Discussion

Confirmation of the hypothesis opens the door for novel therapies to reduce risk. Catalase is ubiquitous and decomposes H_2O_2. Flavonoids are well known to inhibit catalase [16]. Appreciating this, high doses of flavonoids for COVID-19 patients could be beneficial. Non-myeloid cells use chloride ions to produce HOCl. Studies utilizing hypertonic saline for nasal irrigation and gargle (HSNIG) for respiratory infections significantly mitigated the duration of infection as well as reducing viral shedding [17]. Findings from a post-hoc analysis of one of those studies suggest that HSNIG may have a role to play in reducing symptoms and duration of illness in COVID-19 [18]. Endothelin-1 receptor antagonists are therapy for microvascular lung disease. These antagonists could reduce the severity of disease with COVID-19 if the hypothesis is confirmed. Additionally, with this hypothesis, Rho-kinase inhibitors may be beneficial for MVD and should be considered for therapy in high-risk COVID-19 patients [19]. Fasudil is a rho-kinase inhibitor that exerts a cardio-protective function through multiple signaling pathways in animal models of myocardial I/R injury [20]. If serum levels of MPO are high, melatonin is an effective measure to blunt the risk of a myocardial injury or infarct. Melatonin serves as a potent inhibitor of MPO. The trade-off of potentially reducing the innate immune response to COVID-19 would need to be considered. Perhaps the most significant consequence of confirming this hypothesis would be to reinforce the value of preventative measures for arterial disease. Those efforts will reduce the incidence of a significant reason novel infections can be deadly, namely MVD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109999.

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