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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Microvascular disease confers additional risk to COVID-19 infection

Bradley Field Bale\(^a\)^, Amy Lynn Doneena, David John Vigerust\(^b,c\)

\(^a\) Washington State University School of Medicine, Spokane, WA 99204, United States
\(^b\) Vanderbilt University School of Medicine, Nashville, TN 37212, United States
\(^c\) ZDX Health, Scottsdale, AZ 85255, United States

**A B S T R A C T**

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 elderly (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-19
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 peroxide ($H_2O_2$) 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 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].

With this hypothesis, some of the MPO released would not have $H_2O_2$ 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.

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.

References

[1] B. Mullen. ACC CLINICAL BULLETIN COVID-19 Clinical Guidance For the Cardiovascular Care Team. 20202020.

[2] Espinosa V, Rivera A. First line of defense: innate cell-mediated control of pulmonary aspergillosis. Front Microbiol 2016;7:272.

[3] Conti F, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents 2020;34.

[4] Kang SM, Companis RW. Host responses from innate to adaptive immunity after vaccination: molecular and cellular events. Mol Cells 2009;27:5-14.

[5] Sechtem U, Brown D, Godo S, Lanza GA, Shimokawa H, Sidik N. Coronary microvascular dysfunction in stable ischemic heart disease (non-obstructive coronary artery disease and obstructive coronary artery disease). Cardiovasc Res 2020;116:771-86.

[6] Cheng HG, Patel BS, Martin SS, et al. Effect of comprehensive cardiovascular disease risk management on longitudinal changes in carotid artery intima-media thickness in a community-based prevention clinic. Arch Med Sci 2016;12:728–35.

[7] Feng D, Esperat MC, Doneen AL, Bale B, Song H, Green AE. Eight-year outcomes of a program for early prevention of cardiovascular events: a growth-curve analysis. J Cardiovasc Nurs 2015;30:281-91.

[8] Nauseef WM. Myeloperoxidase in human neutrophil host defence. Cell Microbiol 2014;16:1146–55.

[9] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020.

[10] Fielding CA, McLoughlin RM, McLod L, et al. IL-6 regulates neutrophil trafficking during acute inflammation via STAT3. J Immunol 2008;181:2189-95.

[11] Miura H, Bonjak JJ, Ning G, Saito T, Miura M, Gutierrez DM. Role for hydrogen peroxide in flow-induced dilation of human coronary arteries. Circ Res 2003;92:e31–40.

[12] Meuwese MC, Streus ES, Hazen SL, et al. Serum myeloperoxidase levels are associated with the future risk of coronary artery disease in apparently healthy individuals: the EPIC-Norfolk Prospective Population Study. J Am Coll Cardiol 2007;50:159–65.

[13] Thygessen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;138:e618–51.

[14] Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the american heart association. Circulation 2020;141:139-596.

[15] Tagaek VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC, state-of-the-art review. J Am Coll Cardiol 2018;72:2625–41.

[16] Majumder D, Das A, Saha C. Catalase inhibition an anti cancer property of flavonoids: a kinetic and structural evaluation. Int J Biol Macromol 2017;104:929-35.
[17] Ramalingam S, Cai B, Wong J, et al. Antiviral innate immune response in non-myeloid cells is augmented by chloride ions via an increase in intracellular hypo-chlorous acid levels. Sci Rep 2018;8:13630.

[18] Ramalingam B. Hypertonic saline nasal irrigations and gargling should be considered as a treatment option for COVID-19. J Global Health 2020;100:1–4.

[19] Berry C, Sidik N, Pereira AC, et al. Small-vessel disease in the heart and brain: current knowledge unmet therapeutic need, and future directions. J Am Heart Assoc 2019;8:e011104.

[20] Huang YY, Wu JM, Su T, Zhang SY, Lin XJ. Fasudil, a Rho-kinase inhibitor exerts cardioprotective function in animal models of myocardial ischemia/reperfusion injury: a meta-analysis and review of preclinical evidence and possible mechanisms. Front Pharmacol 2018;9:1063.

[21] Galijasevic S, Abdulhamid I, Abu-Soud HM. Melatonin is a potent inhibitor for myeloperoxidase. Biochemistry 2008;47:2668–77.