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Mini Review

Coronavirus Disease (SARS-CoV-2) and Vascular Dysfunction

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Abstract

A novel respiratory virus has developed into a severe killer and has caused unprecedented health and economic crisis worldwide. The standard clinical features of this disease include fever, dry cough, sore throat, headache, fatigue, and breathlessness. Considering that this is a closely related strain of the severe respiratory disease virus, clinicians should make every effort to prevent lung damage and spread of this virus to the vascular system. Age and comorbidities seem to influence the severity of the disease. Odds of death seem to be 7-fold greater for those aged 61 - 80 years; 12-fold higher for those aged 80 years; 24 - 31% greater for those with hypertension, obesity, diabetes, and vascular diseases. We have described this disease as a syndemic disease of cardiometabolic diseases. Because of this syndemic nature, many individuals with metabolic disease risk are developing severe coronavirus disease. Clinical observational studies have shown that individuals with metabolic diseases have compromised vascular and immune systems. This double burden of dysfunctional systems enhances the severity of the coronavirus disease in these COVID-19 patients. Primary prevention by strict adherence to safe public health recommendations and secondary prevention to prevent or reduce viral load at the initial transmission stages were recommended. With the availability of oral antiviral pills, it is possible to prevent the virus from damaging the lungs or the vascular system.

Keywords: *Coronavirus Disease; SARS-CoV-2; Vascular Dysfunction*

Introduction

Chinese researchers have described a cluster of pneumonia cases in Wuhan, China, caused by a novel coronavirus, the 2019 novel coronavirus (2019-nCoV) [1]. The median age of the 41 patients admitted to the hospital was 49, most of them men, less than half had underlying diseases including diabetes (20%), hypertension (15%) and cardiovascular diseases (15%). The UK researchers described COVID-19 as a multisystem disease and did a multicenter cohort study in 302 UK healthcare facilities [2]. Between Jan and Aug 4, 2020, 80,388 patients were included in this cohort study. The cohort's mean age was 71, compared to 49 in the first Chinese studies, and they also found that being male and having at least one underlying health condition was likely to have severe complications. Having at least one underlying health complication was common across all demographic groups, and highest rates in patients aged 60-69, who had two or more comorbidities. Swiss researchers developed a predictive model for predicting critical state, using the US electronic health records (IBM Explorys) data, including demographics, comorbidities, symptoms, and hospitalizations [3]. The interpretability analysis confirmed significant risk factors such as -older age, higher BMI, male gender, diabetes and cardiovascular disease.

Researchers have done a Meta-Analysis on the prevalence of clinical manifestations and comorbidities of coronavirus infection [4]. Of the total of 33 eligible studies, including 7673 infected patients, the most prevalent clinical symptom was fever (84.49%), cough (56.39%), fatigue (33.65%), dyspnea (22.34%), sputum production (22.34%) and myalgia (16.26%). The most prevalent comorbidity was hyperten-

sion (20%), cardiovascular disease (11.9%), and diabetes (9.8%). Other less known comorbidities include excess weight, obesity, chronic kidney disease, chronic liver disease, chronic pulmonary disease, and cerebrovascular disease [5-10]. Researchers who reviewed Data from 6916 patient records from Kaiser Permanente reported that compared to the standard body mass index (BMI) - 18 - 24 Kg/m^2, the risk of death more than doubled for patients with a BMI of 40 - 44 Kg/m^2 and nearly doubled again, for those with a BMI of 45 kg/m^2 or more [11]. These studies demonstrate that even when we consider underlying health conditions, which in most cases enhance the severity of the coronavirus disease, generalizations are tricky. One can only speculate, as the prediction model has shown, age and underlying comorbidities, play a very important role in enhancing the severity of the coronavirus disease.

Severe acute respiratory syndrome (SARS) coronavirus of 2019 (SARS-CoV-2) has a positive-sense RNA genome consisting of 29,000 kilobases with six conserved proteins, polyproteins (pp) pp1a and pp1b, that encompass multiple protein domains, involved in various aspects of coronavirus genome replication; spike protein (S), an envelope protein (E), membrane protein (M) and nucleocapsid phosphoprotein (N). Of these conserved proteins, spike protein is a type 1 transmembrane protein, which plays a vital role in host cell interactions. Virus host entry mediates the transmembrane glycoprotein (S), which forms a homotrimer for binding to the host cell receptor, angiotensin-converting enzyme-11 (ACE2). For all viruses of this group, the S unit is further cleaved by host proteases at the S2 site of the fusion peptide. Because of this transmission mode, coronavirus entry into the host cell is a complex process that requires both receptor binding and proteolytic processing of the S protein to promote virus-cell fusion [12]. According to the experts, the biological processing and activation of coronavirus S-protein to expose the reactive domain also partially explains the phenomenon of COVID-19 with severe cardiovascular damage. Key cell entry mechanism includes higher ACE2 (hACE2) binding affinity of the spike to the receptor-binding domain -reduced dependence on target cell proteases for entry, due to pre-activation by convertase furin [13-15].

Based on the observations of several clinical studies, we and others have described the coronavirus disease as syndemic with cardiometabolic diseases [10,16]. A meta-analysis of five studies by cardiologists of Shandong University, China, reported the presence of comorbidities in Covid-19 patients admitted to hospitals [17]. The overall proportion of comorbidities were hypertension (17.1%), cardiac-cerebrovascular disease (16.4%), and diabetes (9.7%), respectively. In an extensive study of 72,314 patients from China, the authors reported that those who needed hospitalization had underlying conditions, especially hypertension, diabetes, and cardiovascular disease [18,19]. We and others have described coronavirus disease as a disease of the blood vessels, based on the clinical observation reported for severe COVID-19 patients [8,20-22]. The virus attacks the vascular system, which covers an estimated 60,000 miles of blood vessels. The virus also is known to alter platelet and erythrocyte physiology and function. In this invited review, we will describe how a novel animal respiratory virus-transformed itself into a human virus and further evolved to become a virus of the blood components -endothelial cells and platelets.

Coronavirus disease and vascular dysfunction

Human coronaviruses (HCoVs) are responsible basically for respiratory tract infections, causing the common cold. In recent years, severe acute respiratory syndrome virus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) were identified as pathogens of humans. Even these earlier species of coronaviruses were known to have a higher probability of infecting those individuals with some underlying health conditions-indicating the susceptibility of immune-compromised subjects for higher rates of viral infection. Although respiratory viruses primarily infect the respiratory epithelium, it looks more like a portal for entry. The essential steps in alveolar damage were mediated by the endothelial injury resulting in the recruitment of cytokines and chemokines by macrophages, epithelial cells, and endothelial cells. As early as 2003, an outbreak of SARS was reported in China, presenting with fever, acute respiratory distress syndrome (ARDS). Over the years, this novel human respiratory virus has evolved and engineered itself to become a pathogen of the blood vessels and significant vascular system components, including endothelium, platelets, and indirectly the erythrocytes.

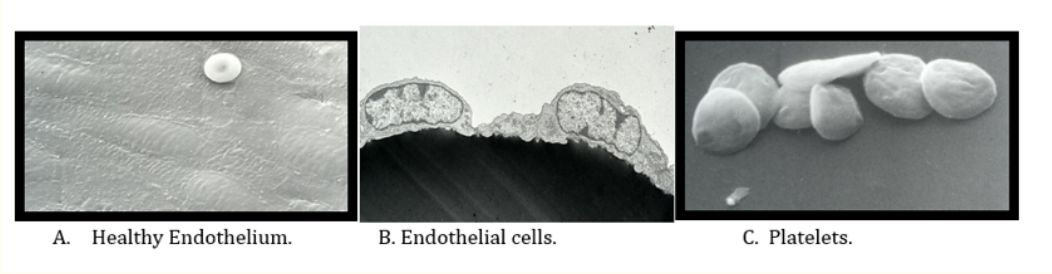

Figure 1: *Electron photomicrographs of the endothelium, endothelial cells, and blood platelets. Courtesy: Professor (Late) James G. White, University of Minnesota).*

A healthy, functioning endothelium (approximately 60,000 miles) keeps the blood vessels relaxed and open to blood flow and its components. Seen above in figure 1 is a photomicrograph of such a healthy endothelium, with no adhering platelets, except for a red cell (Figure 1A). A monolayer of endothelial cells form an interface between the circulating blood and the subendothelium, consisting of cell-matrix components (Figure 1B). Shown also are platelets, which are essential components of the circulating blood (Figure 1C). For the first time, Swiss researchers demonstrated that SARS-CoV-2 infects the host cells using the angiotensin-converting enzyme (ACE) receptors, which are expressed on several organs, including lung, heart, and kidney intestine, and endothelial cells [22]. They also demonstrated the endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19. SARS-CoV-2 infection induces endothelial cell inflammation, leading to endothelins [24]. The viral spike protein binds to ACE2 with greater efficiency than the SARS-CoV-1. The host cell protease TMPRSS2 further facilitates this binding of the S protein to the receptor. Clinical researchers at the First Affiliated Hospital of Xian Jiaotong University, China, have elegantly demonstrated how the viral infection triggers the production of mitochondrial reactive oxygen species, promotes lung injury, downregulates ACE2, impairs the nitric oxide availability, and creates a dysfunctional endothelium [24].

Studies from our laboratory at the University of Minnesota over several decades have demonstrated that dysfunctional or damaged endothelium and exposure of subendothelial matrix components lead to the activation of circulating platelets [25]. We also have shown the bacterial and viral interaction with circulating blood platelets [26]. Elegant studies from our associates at the School of Dentistry demonstrated that aggregation-inducing bacteria contain collagen-like interactive domains (pro-gly-glu-gln-gly-pro-lys) on the surface membranes for interacting with transmembrane signal-transducing integrin domains on blood cells [27]. Chinese researchers have demonstrated that platelets express ACE2 and TMPRSS2, a serine protease for spike protein priming. Furthermore, they have shown that spike protein directly enhances platelet activation and aggregation and promotes a thrombotic state formation [28]. Researchers at Northeastern University have demonstrated that viral binding to cell-surface integrins may contribute to the high level of infectivity. They suggest this possibility, based on the emergence of an RGD tripeptide (arginine-glycine- aspartate) sequence, in the receptor-binding domain of the viral spike protein [29]. There are trillions of circulating platelets, both activated and unactivated platelets, which seem to interact with the virions and viral RNA and could serve as the first blood components to internalize viral particles and introduce them to the circulating blood.

The red blood cells are the third component of the vasculature that plays a vital role in maintaining a healthy functional vascular system. Erythrocytes regulate vascular function by modulation of oxygen delivery, scavenging, and generating vasodilator - nitric oxide. Erythrocyte lysis leads to cell-free hemoglobin, which adheres to the endothelium, can induce hypertension and vasoconstriction [30,31]. In a separate unrelated study, the researchers at Karolinska Institutet, Sweden, found that levels of the small molecule micro-RNA-210

were markedly reduced in red blood cells in patients with type-2 diabetes, compared with red blood cells of healthy subjects. They found that reduction in microRNA-210 caused alterations in specific vascular protein levels and impaired blood vessel endothelial cell function. In laboratory experiments, restoration of microRNA-210 levels in red blood cells prevented the development of vascular injury via specific molecular changes. RBC-bound mitochondrial DNA has been reported to be elevated in individuals with viral pneumonia and sepsis, secondary to coronavirus disease 2019 (COVID-19) and associated with anemia and the severity of the disease. The Toll-like receptors (TLRs) are a class of proteins that play a vital role in the immune system, activating immune responses, such as cytokine production. According to a study, during sepsis and COVID-19, red blood cells had increased amounts of the TLR proteins on their surface [33]. When these cells bind too much to inflammation-causing nucleic acid, they lose their typical structure, causing the body to cease recognizing them. Microphages then remove these blood cells from circulation. Thirty trillion human red blood cells cruise through the bloodstream and supply tissues with oxygen, like circulating platelets may also scan for signs of infection and injury.

Coronavirus disease is an infectious disease of the respiratory system. Coronaviruses' primary mode of entry is via the interaction of spike proteins with insulin-like growth factor-1 (IGF). In animal model's blockage of IGF receptors improves outcome in mouse lung injury [34]. SARS-CoV-2, however, despite its close relationship with the other respiratory viruses, seems to prefer ACE2 as the primary receptor for entry into the cells. Both IGF and ACE2 are expressed abundantly on various cells, including epithelial cells and endothelial cells. The SARS-CoV-2 infection follows a similar transmission pathway -virions from respiratory particles enter the nasal route to the lungs and induce lung injury. The damaged, leaky lung introduces the virus to the vascular bed via the endothelium. Endothelium, the most extensive organ system covering all tissues and organ systems, facilitates the spread of this virus to all regional vascular beds. The typical respiratory virus has turned into a novel bioengineered virus with unique features in its spike proteins. It comes with self-priming capabilities, thus eliminating the need for host proteases for its transmissibility. Spike protein also seems to possess a tripeptide (RGD), which can interact with transmembrane integrin cell signal processing domains of various cells, including circulating platelets. Damaged endothelium promotes platelet activation, which in turn encourages virion binding through their RGD sites. Activated platelets can introduce the virions to all the regional vascular beds. The compromised endothelium is deprived of vasodilators, damage of RBCs deprive oxygen; free hemoglobin released will scavenge nitric oxide and induce endothelial dysfunction.

Primary and secondary prevention of coronavirus disease

To date there is a lack of cure for this disease. The major efforts for primary prevention were focused on public health safety measures and vaccine development. Tremendous progress was made in vaccine development. Currently, there are several approved vaccines available for use against COVID-19. Despite the availability of the vaccines, their distribution has remained inequitable. These inequities of vaccine distribution have billions of individuals vulnerable to the deadly virus. Globally, over 3 billion individuals are 'at risk' for severe coronavirus disease, as they all have one or the other metabolic disease as comorbidity. In the absence of a natural cure for this disease, primary prevention strategies will include the strict following of public health safety measure mandates, such as using face masks, handwashing with soap, isolation, and quarantine of infected individuals, and avoiding the use of super spreader events. There are already a variety of nasal sprays in the market (VIRALEZE, Nasitrol, COVIXYL-V), that claim to prevent or reduce viral load in the nasal passage. Currently, they are undergoing testing in many different countries. Merck (Molnupiravir) and Pfizer (Plaxlovid) have come up with already approved oral antiviral drugs as repurposed drugs for COVID-19. They claim a greater than 80% reduction in the severity of the disease in those covid-patients who took a course of these oral antiviral pills. Because of this early success in repurposing approved drugs for COVID-19 management, there is a great interest in drug discovery and the development of new antiviral drugs [35].

Conclusion

Coronavirus which was discovered in Wuhan, China, in late 2019, has spread worldwide and caused severe health and economic damage. The novel virus, a classical respiratory virus, has evolved into a formidable killer by taking advantage of the compromised vascular

and immune systems in aged COVID-19 patients with comorbidities such as hypertension, excess weight obesity, diabetes, and vascular disease. We have described how this respiratory virus has adapted to change its host preference to ACE2 receptors on endothelial cells and circulating platelets. The changes in its spike proteins, self-priming capabilities, and selection of a receptor that is abundantly expressed on the endothelium have facilitated the virus to move from respiratory epithelial cells to the vast surface of the vascular endothelium and gain access to every tissue and organ in the human body. The epidemic of metabolic diseases has been on the rise for the last four decades. Coronavirus pandemic has taken advantage of this current pandemic of metabolic disorders. We will have to live with these two syndemic diseases for some time to come.

Since there is no cure for these conditions, primary and secondary prevention of coronavirus is the only option we have. Public health experts have advocated best health practices such as masks, hand washing, and safe social distancing. It has worked in many countries. However, we need other interventions which are reliable. Pharma companies have developed nasal sprays to prevent or kill the virus during its entry through nasal passages. Merck and Pfizer have developed promising antiviral pills for managing the severity of the disease. If the clinical data obtained by these drug companies hold good, then these oral pills are as effective as vaccines in preventing hospitalization and death. Another good news is that these drug companies allow developing countries to produce their oral antiviral medications under separate licenses. One of the several Biden Administration COVID rescue efforts, the American Rescue Plan, is investing more than 3 billion USD to accelerate the discovery, development, and manufacture of certain antiviral medicines as an initiative of the Whole-of-Government strategy to develop the next generation of COVID-19 therapeutics.

Bibliography

1. Huang C., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *Lancet* 395.10223 (2020): 497-506.

2. Drake TM., *et al*. "Characterization of in-hospital complications associated with COVID-19 using the ISARIC WHO clinical characterization protocol: a prospective, multicenter cohort study". *Lancet* 398.10296 (2021): 223-237.

3. Rinderknecht MD and Klopfenstein T. "Predicting critical state after COVID-19 diagnosis: model development using a large US electronic health record dataset". *NPJ Digital Medicine* 113 (2021).

4. Noor FM and Islam M. "Prevalence of Clinical Manifestations and Comorbidities of Coronavirus (COVID-19) Infection: A Meta-Analysis". *Fortune Journal of Health Sciences* 3 (2020): 55-97.

5. Rao GHR. "COVID-19 and Cardiometabolic Diseases.: Guest Editorial". *EC Cardiology* 7.6 (2020): 08-12.

6. Rao GHR. "Coronavirus (COVID-19), Comorbidities, and Acute Vascular Events; Guest Editorial". *ECCMC EC Clinical Case Reports* 3.6 (2020): 87-91.

7. Coronavirus Disease (Covid-19), Comorbidities, and Clinical Manifestations. Guest Editorial". *EC Diabetes and Metabolic Research* 4.6 (2020): 27-33.

8. Rao GHR. "Coronavirus Disease (Covid-19): A Disease of the Vascular Endothelium". *Nature Cardiovascular Research* 2.1 (2020): 23-27.

9. Rao GHR. "SARS-CoV-2 biochemistry, Transmission, Clinical Manifestations and Prevention". *International Journal of Biomedicine IJBM – DOAJ* 10.4 (2020).

10. Rao GHR. "Twindemic of Coronavirus Disease and Cardiometabolic Diseases". *International Journal of Biomedical Science* 11.2 (2021): 111-122.

11. Tartof SY., *et al*. "Obesity and Mortality among patients diagnosed with Covid-19: Results from an Integrated Health Care Organization". *Annals of Internal Medicine* (2020).

12. For all viruses of this group, S unit is further cleaved by host proteases, at the S2 site of the fusion peptide. Because of this mode of transmission, coronavirus entry into the host cell is a complex process, that requires both receptor binding and proteolytic processing of the S protein, to promote virus-cell fusion.

13. Hoffman M., *et al*. "SARS-Cov-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor". *Cell* 181 (2020): 271-280.

14. Liu W., *et al*. "Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV". *ChemBioChem* 21.5 (2020): 730-738.

15. Shang J., *et al*. "Cell entry mechanism of SARS-CoV-2". *Proceedings of the National Academy of Sciences of the United States of America* 117.21 (2020): 11727-11734.

16. Rao GHR. "Syndemic of Coronavirus Disease and Metabolic Diseases: A Global Perspective and Call for Action". *Case Reports* 6.4 (2021): 28-32.

17. Wang B., *et al*. "Does comorbidity increase the risk of patients with COVID-19: Evidence from Meta-Analysis. Meta-Analysis". *Aging (Albany NY)* 12.7 (2020): 6049-6057.

18. Wu Z and McGoogan JM. "Characteristics and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center of Disease Control and Prevention". *The Journal of the American Medical Association* (2020).

19. Adao R and Guzik TJ. "Inside heart of COVID-19". *Cardiovascular Research* 8 (2020): cvaa086.

20. Rao GHR. "Coronavirus Transmission, Vascular Dysfunction and Pathology". *Journal of Cardiology Research Reviews and Reports* 1.3 (2020): 1-4.

21. Rao GHR. "Clinical manifestation of coronavirus disease as it relates to cardio-vascular health". *Frontiers in Cardiovascular Medicine* 1.1 (2020): 20-103.

22. Varga Z., *et al*. "Endothelial cell infection and endotheliitis in COVID-19". *Lancet* 395.10234 (2020): 1417-1418.

23. Griffiths CD., *et al*. "IGF1R is an entry receptor for respiratory syncytial virus". *Nature* 583 (2020): 615-619.

24. Lei Y., *et al*. "SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE2". *Circ* 128.9 (2021): 1323-1326.

25. Rao GHR. "Influence of anti-platelet drugs on platelet-vessel wall interactions". Prostaglandins, *Leukotrienes and Essential Fatty Acids – Journal* 30 (1987): 133-145.

26. Clawson CC., *et al*. "Platelet interaction with bacteria. 1V. Stimulation of the release reaction". *The American Journal of Pathology* 81.2 (1975): 411-420.

27. Herzberg MC. "Platelet-streptococcal interactions in endocarditis". *Critical Reviews in Oral Biology and Medicine - SAGE Journals* 7.3 (1996): 222-236.

28. Zhang S., *et al*. "SARS-Cov-2 bind platelet ACE2 to enhance thrombosis in COVID-19". *Journal of Hematology and Oncology* 13.120 (2020).

29. Makoswki L., *et al*. "Biological and clinical consequences of integrin binding via a rogue RGD motif in the SARS CoV-2 spike protein". *Viruses* 13.2 (2021): 146.

30. Rifkind JM., *et al*. "Editorial: Regulation of Vascular Function by Circulating Blood". *Frontiers in Physiology* (2019).

31. Helms CC., *et al*. "Erythrocytes and Vascular Function: Oxygen and Nitric Oxide". *Frontiers in Physics* (2018).

32. Zhou Z., *et al*. "Downregulation of erythrocyte miRNA 210 induces endothelial dysfunction intype-2 diabetes". *Diabetes* (2021): db210093.

33. MathewLam LK., *et al*. "DNA binding to TLR9 expressed by red blood cells promotes innate immune activation and anemia". *South Carolina Clinical and Translational Research Institute* 13.616 (2021).

34. Choi JE., *et al*. "Insulin-like growth factor-1 blockade improves outcome in a mouse model of lung injury". *American Journal of Respiratory and Critical Care Medicine* 179 (2008): 212-219.

35. Filmore N., *et al*. "Disulfiram use is associated with lower risk of COVID-19: A retrospective cohort study". *PLOS ONE* (2021).

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