FM Publisher
Frontiers Journal of Cardiology & Cardiovascular Medicine (FJCCM)
Volume 01, Issue 01, Article ID FJCCM-20-103

Editorial *Open Access*

CLINICAL MANIFESTATIONS OF CORONAVIRUS DISEASE AS IT RELATES TO CARDIO-VASCULAR HEALTH

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Citation: Rao, G.H.R., (2020). Clinical Manifestations of Coronavirus Disease as it Relates to Cardio-Vascular Health. *Frontiers Journal of Cardiology & Cardiovascular Medicine*, 1(1), 1-07.

Received Date: *12 November 2020;* ***Accepted Date:*** *15 November 2020;* ***Published Date:*** *23 November 2020*

EDITORIAL ARTICLE

SARS-CoV-2, -a novel killer virus, was first reported in Wuhan City, China, in December of 2019. The virus genome was characterized by the Chinese researchers and reported to the World Organization(WHO) in late January of 2020. Following this report, the WHO declared a "public health emergency of international concern (Kamps, B. S., 2020)." This novel coronavirus has caused an unprecedented syndemic worldwide. Global cases of Covid-19 is more than 50.7 million, and number of COVID related deaths, is more than 1.26 million (coronavirus.jhu.edu/map.html). In the US, the number of infected individuals, has exceeded 10 million and COVID-related deaths, to more than 237,860. Currently, US is reporting more than 100, 000 cases of COVID-19 positive cases per day. The viral genome is 29.8 kilobase, containing six major open reading frames. The most common clinical symptoms of coronavirus disease (COVID-19) are fever, cough, fatigue, shortness of breath, muscle ache, headache, chest pain, diarrhea, vomiting, sore throat, and sputum production (Xie et al., 2020; Guan et al., 2020; Jiang et al., 2020; Wang et al., 2020; Zhang et al., 2020; Xu et al., 2020). The common mode of transmission is through the respiratory particles. The incubation period for viral replication is 3 to 7 days. Spike (S) proteins are of vital importance, in terms of viral infectivity as well as antibody targets. Both the S-glycoprotein and ACE2 receptor, are known to be extensively glycosylated. Spike protein has been shown, to contain 66 glycosylation sites, suggesting the importance of understanding the role of glycosylation, for the development of new vaccines (Korber et al., 2020; Novokmet et al., 2020). It has been reported, that angiotensin-converting enzyme-2, is the main host cell receptor of human pathogenic coronavirus (Mehta & Alter, 2017). ACE2 is expressed by

epithelial cells of the lung, intestine, kidney and blood vessels (Zhang et al., 2020). Circulating ACE2 enzyme seems to offer protection, against influenza A(H7N9) virus-induced lung injury (Ciaglia et al., 2020). Viral entry is facilitated by the presence of ACE2 as well as TMPRSS2 protease activity. Sungnak and associates have co-detected, these transcripts in specific respiratory and corneal epithelial cells, potentially explaining the high efficiency of SARS-CoV-2 transmission (Hamming et al., 2004; Yang et al., 2014; Xu et al., 2020; Sungnak et al., 2020).

The clinical manifestations of COVID-19, according to the latest reports, seem to be heterogenous (Xie et al., 2020; Guan et a., 2019; Jiang et al., 2020; Wang et al., 2020; Zhang et al., 2020; Xu et al., 2020). Researchers from academic hospitals at Wuhan, China, have reported that of the 416 covid-19 patients admitted, 20% had evidence of myocardial injury, evidenced by the presence of elevated levels of cardiac troponin-1 (Guo et al., 2020; Shi et al., 2020). The authors speculated, that inflammation may be a potential mechanism, for myocardial injury and suggested aggressive treatment of patients 'at risk' for myocardial injury. The most common pattern of coagulopathy, observed in patients with COVID-19, is characterized by elevations in fibrinogen and D-dimer levels. These observations parallel rise in markers of inflammation, - elevated levels of C-reactive protein, proinflammatory cytokines, - IL1B, IFNλ, TNFα, IP10 and MCP1 (Guan et al., 2019). Unlike sepsis mediated disseminated intravascular coagulation (DIC), the degree of activated partial thromboplastin (aPT) elevation is less than partial thromboplastin (PT) elevation. According to some researchers, a hallmark of severe COVID-19 coagulopathy, -in 71.4% of patients who died of COVID-19 met, ISTH criteria for DIC (Kollias et al., 2020; Bikdeli et al., 2020). The observed coagulopathy, seems to be predominantly pro-thrombotic DIC, with high venous thromboembolism rates, pulmonary congestion, microvascualr thrombosis, reduced capacity to cleave and remove fibrin, with high rates of central line thrombosis, and vascular occlusive events (ischemic limbs, strokes). Researchers from the University of North Carolina demonstrated, that elevated levels of fibrin are the landmark of acute lung injury, and in COVID-19 infection, -dysregulation of urokinase pathway, contributes to more severe lung pathology, and serpin-1 plays a protective role following infection (Gralinski et al., 2013).

Following infection and viral replication, downregulation of ACE2 enzyme occurs, resulting in dysfunction of the angiotensin system, resulting in hypokalemia, vasoconstriction, and development of acute respiratory distress syndrome (ARDS). Endothelium is the largest organ of the body, covering a large surface area, and reaching out to every tissue and organ. As such, the injury to the endothelium could introduce a cascade of events, leading to platelet activation, thrombin generation, and promotion of both thrombotic and thrombolytic events. Just to distinguish the term 'vascular disease' from the vascular damage and pathology observed in the severely ill COVID-19 patients, we refer to this condition as a 'disease of the blood vessels' (Rao, 2020; Rao, 2020). In majority of cases, the severity of the coronavirus disease has been found to be associated, with pre-existing comorbidities, which includes metabolic diseases such as hypertension, obesity, diabetes, and vascular diseases (Rao, 2020). Those with such diseases, or with elevated risk factors for such diseases, -will have a compromised endothelium, favoring endothelial dysfunction. The infection of endothelium by SARS-CoV-2 seems to add to this problem, by further damaging the endothelium, causing dysfunction, disruption of vascular integrity, and endothelial cell death. These events lead to the exposure of thrombogenic basement membrane, and results in the activation of thrombotic and clotting cascade.

Nearly one-fourth of those hospitalized with COVID-19, have been diagnosed with cardiovascular complications, which have been shown to contribute roughly to 40% of all COVID-19 related deaths. A JAMA Cardiology study used MRIs on 100 people, who had recovered from COVID-19 within the past two months. They found abnormalities in the

hearts of 78% recovered patients and "ongoing inflammation" in 60%. They also found high levels of troponin, an indicator of heart damage, in 76% of the patients tested (Puntmann et al., 2019). The mechanism of cardiac injury in COVID-19 is poorly understood. Earlier studies indicated, diffuse alveolar damage and pulmonary and microangiopathic changes. Viral infection of the endothelial tissue has been reported. The effect of cytokine storm, specifically with interleukin- 6 and interleukin -8 seem to modulate platelet activation, neutrophil recruitment and trapping, and hypercoagulable state of the blood. Neutrophil extracellular traps (NETs), seem to contribute to microthrombi, through platelet-neutrophil interactions in COVID-19 acute respiratory distress syndrome. Neonatal NET-inhibitory factor (nNIF) has been shown to block NET formation induced by COVID-19 plasma (Middleton et al., 2020). It is well known, that excessive inflammation from an overactive immune system response, can initiate the clot formation in severely ill COVID patients. Autoantibodies generated in response to the viral infection, instead of recognizing the foreign invader, seem to go after molecules that form cell membranes. Such attacks may prompt immune cells called neutrophils, to release a web of genetic material that traps the virus particles outside of the cells. Presumably, in the tissues this seems to be the way to control infections, but in the blood stream, it triggers thrombotic episodes (Zuo et al., 2020).

When reviewing the effects of coronavirus, on clinical manifestations related to the heart , brain and the blood vessels, we will have to discuss the acute effects, as well as chronic effects that linger on, even after full recovery from this disease. Heart conditions associated with COVID-19 include, inflammation and damage to heart muscle, -known as myocarditis, which may impair the heart's ability to pump blood and send electrical signals. Whereas, inflammation of the covering of the heart, -known as pericarditis, may cause sudden onset of chest pain, may also be felt in shoulders sand neck. "Although more research needs to be done to understand the long-term effects of COVID-19 on the heart, we do know COVID-19 effects the heart in two ways, "says Dr. Bhudev Sharma, a Cardiologist at JFK Medical Center, Edison, NJ. First it can directly cause myocarditis and blood clots, and second, it can indirectly affect the heart by making existing conditions worse. Talking about indirect effects, we can also speculate, the long-term effect of chronic stress of this unprecedented syndemic on heart health. In an earlier article, we articulated the effect of COVID-19 related anxiety, stress, and fear, on heart health (Rao, 2020). Researchers from Cardiovascular Center, Division of Cardiology, Tufts Medical Center, Boston, summarize their concerns in the July (2020) issue of JAMA under the title, - "Fear of Coronavirus Disease 2019-An Emerging Cardiac Risk." "While early fears of widespread death and overwhelmed hospitals, have played an important role in sounding alarm about this pandemic, and motivated important social distancing measures, these fears are also causing substantial harm. In this Viewpoint, using cardiac disease as an example, we explore the hazards associated with the pandemic and initial response." The authors continue, - "We argue that clinician's ability to modulate fear-a sensitive but nonspecific response to threats, - will be a major determinant of the magnitude of the pandemic's effects" (Wessler et al., 2020).

"If you start to put all of the data together that's emerging with this novel disease, it turns out that this virus is probably vasculotropic virus, meaning that it affects the blood vessels," says Dr. Mandeep Mehra, Medical Director of the Brigham and Women's Hospital and Vascular Center. In an article published in the Journal Lancet, the authors explain how the SARS-CoV-2 virus can infect the endothelial cells that line the inside of the blood vessels. A monolayer of endothelial cells (Fig. 1) cover the entire surface of the blood vessels and protect the cardiovascular system, and they release bioactive modulators, as well as

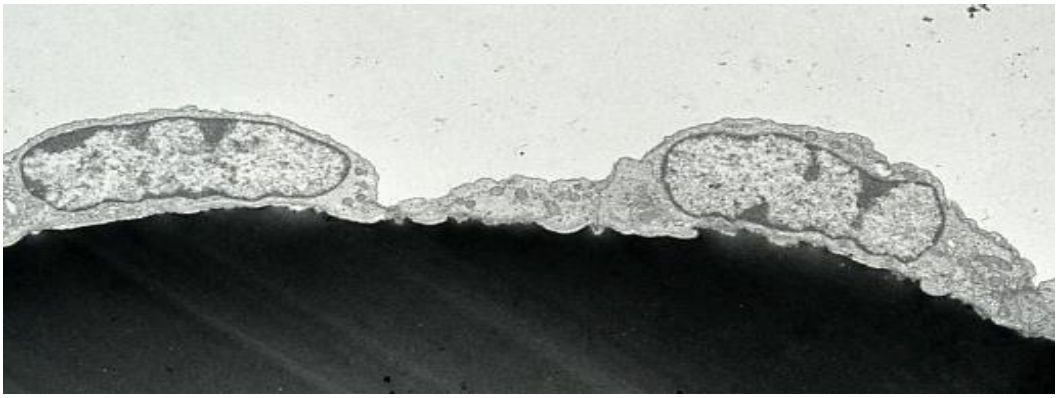

Fig. 1. Endothelial Cells covering the vascular surface. (Courtesy: Late Prof. J.G. White).

proteins that influence everything from various activation mechanisms, of platelets and coagulation cascade as well as immune response. Endothelium is the largest organ of the body, covering a large surface area, and reaching out to every tissue and organ. As such, the injury to the endothelium could introduce a cascade of events, leading to platelet activation, thrombin generation, and promotion of both thrombotic and thrombolytic events. Those with metabolic diseases, or with elevated risk factors for such diseases, -will have a compromised endothelium, favoring endothelial dysfunction. The infection of endothelium by SARS-CoV-2 seems to add to this problem, by further damaging the endothelium, causing dysfunction, disruption of vascular integrity, and eventually endothelial cell death. These events lead to the exposure of thrombogenic basement membrane, and results in the activation of thrombotic and clotting cascade. In view of these observations, critical care clinicians recommend aggressive anti-thrombotic and thrombolytic therapies in the management of acute COVID-19 cases.

SARS-CoV-2 virus that causes coronavirus disease, shares many biological features with SARS-CoV, the virus that causes acute respiratory syndrome, because of its genomic sequence similarity, yet differs considerably, -when it comes to infection, transmission, pathogenicity, clinical manifestations and disease severity. The degree of severity increases with the age of the hosts and coexisting conditions. The fact that the major host receptor is the angiotensin converting enzyme 2 (ACE2), -the ubiquitous nature of this receptor in the host (especially in endothelial cells and fat cells), and the down regulation of this enzyme leads to a host of altered vascular function. Furthermore, those with metabolic comorbidities such as hypertension, excess weight, obesity, diabetes and vascular diseases with pre-existing vascular dysfunction, seem to have increased severity of the disease as well as COVID-19 associated mortality. Stanford researchers from the Division of Cardiovascular Medicine, in their review in Nature, conclude, “Mechanistically, the interaction between the S protein and ACE2 is likely to have a central role in disease pathogenesis, especially in cardiovascular manifestations of this disease, and this interaction is potential target for the prevention and treatment of COVID-19 (Nishiga et al., 2020).

Using the SARS-CoV-2 spike protein as a bait, Dr Sriram Subramaniam of the University of British Columbia found a potential neutralizing antibody for this virus. They have isolated smallest biological molecules, which can interact with the Spike (S) protein of this virus, from a pool of 100 billion potential candidates. The drug known as Ab8, does not bind human cells but can be used as both therapeutic, as well as protective candidate against SARS-CoV-2 virus. When the US President was found to be COVID-19 positive, an experimental monoclonal antibody cocktail manufactured by Regeneron (REGN-CoV-2) was successfully used. Pandemic Prevention Platform (P3), at the Defense Advanced Research Project agency has a novel approach, in which they aim to develop monoclonal antibodies,

that can be made by the body itself, instead of in large fermentation tanks. The idea, which has not been tested in humans for COVID-19, is to inject people with DNA or messenger RNA (mRNA), that encodes a desired antibody, allowing their own cells to make it. “Today is a great day for Science and humanity” Pfizer CEO Albert Bourla said on Monday (36). Pfizer and BioNTech announced an mRNA-based vaccine candidate against COVID-19, which has achieved success in first interim analysis from phase 111 study (November 9, 2020). Pfizer said that the vaccine, made with German partner BioNTech, had an efficacy rate higher than 90% at seven days after the second dose. Pfizer will seek emergency authorization within a week. Moderna Inc., of USA, has a similar mRNA vaccine under phase 111 clinical study, and plans to supply 90 million doses to European Union. The US FDA has just given emergency approval to an experimental antibody treatment for COVID-19 made by Eli Lilly, which is like the Regeneron cocktail.

In the absence of a definite cure, currently the only safe option we all have is, -to adhere to the public health best practices, wearing of masks, social distancing, contact tracing and containment of infected individuals till they are free of infection.

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