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Coronavirus Transmission, Vascular Dysfunction, and Pathology

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Coronavirus (SARS-CoV-2) has spread rapidly, to over 200 countries world-wide, and has caused unprecedented public health and economic crisis. This public health crisis is nowhere in the world greater, than in the most advanced nation, - the United States of America. As of this writing, there are over 4 million reported cases of infection, and145,000 deaths. In some southern states, test positive rates are as high as 25%. Nation's top infectious disease expert, Dr Anthony Fauci has been on the news, constantly advocating, social distancing, facial coverage, hand washing, and other public health best practices. On the other hand, our expert from the Midwest, Professor Michael Osterholm of the University of Minnesota, initially advised us to hide from the virus,-"if the virus cannot find you, you will not get the disease," Just this morning, he was on the national TV heralding the bad news, -the coronavirus will never go away, -"like HIV, will stay with us forever." These days, no news is good news, and no one seems to agree on any news, related to the coronavirus; infection, transmission, disease progress, immunity or the severity. Individuals with pre-existing conditions, such as hypertension, excess weight, obesity, type-2 diabetes and vascular diseases, are at a higher risk to experience severity of this disease, than healthy individuals. In this guest editorial, we are going to discuss three specific areas of coronavirus disease; infection, transmission, vascular damage and pathology.

Coronaviruses are relatively large viruses (125 nanometers), with 30,000 genetic bases, -the largest genomes of all RNA viruses. In addition, they are bestowed by a genomic proof-reading mechanism, -which keeps the virus from accumulating unwanted mutations. According to the experts, SARS-CoV-2 can mix the transmissibility of the common cold (affecting the throat), with the lethality of MERS-CoV and SARS-CoV. SARS-CoV-2 can shed viral particles from the throat, to saliva in asymptomatic individuals. Of the four viruses of great concern, two of them attack upper respiratory tract, whereas MERS-CoV and SARS-CoV are successful in infecting lung cells. SARS-CoV-2 on the other hand, can attack both the areas efficiently, hence has a better foothold on sties of infection. The virus latches on to a receptor called ACE2, which is found on the lining of the arteries and veins, that are the major supply routes, to all the organs of the body. Yet another enzyme, 'Furin" also seems play a role in cleaving the viral spike protein. Both the enzymes, angiotensin 11, and furin, are abundant throughout the body, and facilitate the transmission of the virus from cell to cell, as well as person to person (Cyranoski D: Profile of a Killer Virus. Nature 581, 22-26, 2020). Furin is known to be involved in the cleavage of a wide variety of proteins and is expressed ubiquitously.

Angiotensin converting enzyme-2 (ACE2) like furin, is a type 1 integral membrane protein. This enzyme is found in most tissues, with highest expression in the cardiovascular system, gut, kidneys and lungs. In the vascular system, ACE2 is expressed in cardiomyocytes, epicardial adipose tissues, cardiac fibroblasts, vascular smooth muscle cells and endothelial cells [1, 2]. Abnormal activation of the renin-angiotensin system (RAS) contributes, to the development and progression of atherosclerotic vascular disease, by promoting inflammation, endothelial dysfunction, oxidative stress, smooth muscle migration and proliferation [2, 3]. In addition to these roles, it serves as receptor for the transmission of the severe acute respiratory syndrome-coronavirus (SARS-CoV) and SARS-CoV-2 viruses, providing a critical link between immunity, inflammation, and cardiovascular disease [4-8]. According to Hoffman and associates, ACE 2 is a membrane-anchored carboxypeptidase, highly expressed by airway epithelial cells, acts as the primary cell entry receptor for SARS-CoV virus [9]. A clinically proven serine protease inhibitor, camostat mesylate, inhibits the activity of transmembrane protease serine 2 (TMPRSS2) and blocks SARS- CoV-2 infection in lung cells. Non-acetylated sialo side attachment receptors expressed by glycoproteins and glycolipids on the host are the targets of virus, -small fragment of the S1 region, receptor binding domain (RBD), binds with the peptidase domain of ACE2 [10]. Once the spike protein is attached, the internalization of the virus is promoted by hemagglutinin cleavage, modulated by the TMPRSS2, a cell surface expressed protein by epithelial cells. Once the virions thus released fuse with the membrane, ACE 2 expression seems to get downgraded, resulting in excess production of angiotensin, and enhancing oxidative stress mechanisms [11]. Canadian researchers have described a bifunctional role for the ACE2 and called it a "double- edged sword' as it can turn off the RAS system and exert beneficial effects and at the same time, offer unique susceptibility to lung and vascular disease in Covid-19 patients [12].

It is of great interest to note, that both the S-glycoprotein (Spike Protein) of the SARS-CoV-2 and ACE2 receptor are known to be highly glycosylated. Spike glycoprotein seems to contain

66 glycosylation sites [13]. The spike protein consists of two functional units, S1 and S2 and the receptor binding domain (RBD), which resides within the S1 subunit. Spike proteins that protrude from the viral envelope, constitute the main target of neutralizing antibodies, as well as possible pharmacological interventions [14, 15]. For instance, well known antiviral drug, Tamiflu, is directed towards inhibiting the enzyme, that cleaves sialic acid on the surface of human cells. Even the controversial drug, hydroxychloroquine, chloroquine, and well know antiviral drug, remdesivir (GS-5734), efficiently inhibit SARS-CoV-2 infection in vitro by altering the glycosylation profile of ACE2 receptor and spike proteins [16]. Ragon Institute (MGH, Harvard & MIT, Boston) researchers, Dr Mehta and associates have proposed opportunities to exploit antibody glycosylation in improving vaccines [17]. The receptor binding domain found at the Spike Protein recognizes the human angiotensin-converting enzyme 2(hACE2). Thermodynamic studies done by the Theoretical Chemistry Group, Universidade Federal do Rio Grande do Sul, Brazil, report that chemical affinity of the new SARS-CoV-2 for the hACE2 enzyme virus is much higher than the 2002 SARS-CoV. These observations explain the chemical reason for the difficulty in treating the SARS-CoV-2 virus using drugs targeting Spike Protein, as well as helps to explain its infectivity, while defining a minimum free energy of binding, for new drugs to be designed against this disease [18].

In 1982, Sune K. Bergstrom, Bengt I. Samuelsson and John R. Vane were awarded Noble Prize in Physiology and Medicine, for their discoveries concerning prostaglandins and related biologically active substances. Prostaglandins (PG), PGG2, PGH2, Thromboxane (vasoconstrictor and Platelet agonist), and Prostacyclin (vasodilator and antiplatelet compound), play a very important role in vascular physiology, function, and pathology. One of the co-recipients of this prestigious award, Professor John R. Vane, not only discovered prostacyclin, but also made the fundamental discovery, that anti-inflammatory compounds such as aspirin, act by blocking the formation of prostaglandins and thromboxanes. We at the University of Minnesota, demonstrated a short-acting drug, ibuprofen and an irreversible inhibitor of cyclooxygenase, aspirin, exert their inhibitory effect by interfering with heme-arachidonic acid interaction [19]. In a one of a kind studies, we demonstrated that exposure of cyclooxygenase first to short-acting ibuprofen, prevents irreversible inhibition of this enzyme by aspirin, once the active site is occupied by ibuprofen. We strongly feel, that like this drug-enzyme interaction, interaction with the angiotensin 2 enzyme with the SARS-CoV-2, could be prevented by exposure of this enzyme by chloroquine, hydroxychloroquine prior to the virus infection, despite CoV-2's high thermodynamic affinity to the binding site [20]. Indeed, *in vitro* studies with Vero E6 cells have demonstrated, that when exposed to chloroquine or hydroxychloroquine prior to infection, these drugs effectively prevent the subsequent viral infection [21, 22]. Hoffman and associates in a recent article, report that although chloroquine has been shown to inhibit SARS- CoV-2 infection *in vitro* in some cell lines, it does not inhibit infection of human lung cells by coronavirus-2019 (Nature: July 22, 2020) https://doi.org/10.1038/s41586-020-2575-3).

Angiotensin 11 (Ang 11) causes vasoconstriction and exerts multiple biological functions. Capillary blood vessels in the lungs are one of the major sites of ACE expression. Studies by researchers at the Johns Hopkins University, has demonstrated that Ang 11 stimulates expression of proinflammatory mediators, such as interlukin-8/Cytokine-induced Neutrophil Cehmoattractant-3, and interleukin-6 via both receptor types (AT1R & AT2R). Activation of AT1R seems to modulate expression of transcription factors NF-kB and activating protein 1(AP1). SARS-CoV-2 spike protein binding to ACE2, down regulates the ACE2 protein expression, leading to elevation of Ang11 levels, and increased vascular permeability. Furthermore, ACE 2 modulates neutrophil infiltration in the lung. Several studies have demonstrated neutrophil traps (NETs) as markers of disease severity and thrombotic conditions in Covid-19 patients [23-25]. Increased neutrophil-to-lymphocyte ratio seems to predict severity of the Covid-19 related illness in the early stages of the disease. Neutrophil nets seem to promote development of larger aggregates, 'AggNETs', that activate platelets, facilitate thrombin production, and formation of microthrombi in blood vessels. The extracellular components released by the NETs activate platelets, which further promote the formation of NETs and initiate a thrombotic condition [26].

According to the experts, 40% of deaths from Covid-19, are related to cardiovascular complications. In view of this observation, we and others, have speculated that Covid-19, unlike the SARS-CoV, looks like a vascular disease than purely a respiratory one [27]. The expression of ACE2 on vascular endothelium, smooth muscle cells, and perivascular pericytes suggests, that the virus once infects the vascular system, -can spread easily throughout the body, to all the organ systems [27]. Ackerman and associates, at the Harvard Medical School, studied lungs obtained from autopsy of patients, who died from Covid-19 infection. They found severe endothelial injury, associated with intracellular SARS-CoV-2 virus and disrupted endothelial membranes. They also found, widespread vascular thrombosis with microangiopathy, and occlusion of alveolar capillaries [28-30]. In view of these observations, experts are of the opinion, that stabilizing the endothelial function (anti-inflammatory drug therapy, steroids, statins, prostacyclins) could be very relevant for vulnerable patients, with pre-existing endothelial dysfunction (individuals with cardiometabolic diseases). According to the International Society on Thrombosis and Haemostasis (ISTH), emerging research on Covid-19 indicates; patients with COVID-19 pneumonia, who are hospitalized, have higher incidence of venous thromboembolism (VTE). Covid-19 pneumonia is associated with marked hyper coagulopathy, with elevated levels of fibrinogen and D-dimer. They also have major inflammatory response, which can lead to micro clots-immunothrombosis-within the lungs.

A special report published by the Radiological Society of North America (Apr 23, 2020), stresses that careful attention needs to be paid to the initial diagnosis, and treatments of the prothrombotic state, that may be precipitated in substantial number of COVID-19 patients. According to Professor Edwin J.R. van Beek, director of Edinburgh Imaging, the Queens Medical Research Institute, at the University of Edinburgh, UK, "Imaging and pathological investigations confirmed, that the COVID-19 syndrome is a thrombo-inflammatory process, initially affecting the lung perfusion, but consecutively affecting all organs of the body. No wonder, William Li, President of the Angiogenesis Foundation says, "We see blood clotting, we see kidney damage, we see inflammation of the heart, we see stroke, we see encephalitis." Mandeep Mehra, Medical Director at the Brigham and Women's Hospital Heart and Vascular Center says, that the SARS-CoV-2 virus is probably vasculotropic, -meaning that it affects blood vessels. He continues, "The concept that's emerging is that this is not a respiratory illness alone, this is a respiratory illness to start with, but it is actually a vascular illness, that kills people with its involvement of the vasculature." Experts agree that pre-existing conditions, such as hypertension, obesity, type-2 diabetes and vascular diseases, puts patients to high risk with Covid-19. All

these diseases cause endothelial dysfunction, and the additional damage by the SARS-CoV-2, could cause serious problems [31].

In the July issue of NEJM (July 17, 2020), Fanny Burel-Vandenbos and associates of University Hospital, Nice, France, discuss about the findings of Ackerman et al from the Harvard Medical School (NEJM May 21st, 2020) reported under the title. "Pulmonary Vascular Pathology in Covid-19 [32]. Ackerman and associates hypothesized in their report, that mechanism responsible for the observed vasculopathy, was a direct viral effect on endothelial cells or perivascular inflammation [30]. According to the French researchers, Pericytes are perivascular cells, that have a key role in the maintenance of micro vessel integrity [32]. They also speculate that, because they have the highest expression of ACE2, -pericytes, could be a target for the virus. In reply, the Harvard researchers comment, "As previously suggested, vascular injury leading to abnormal vasoregulation and vascular shunting may be one explanation, for the presence of hypoxemia. According to some studies, there seems to be a massive demand for porphyrins for SARS virus to survive. SARS-CoV-2 exhibits an unusual affinity to 1-β chain of hemoglobin and such interactions, impair the ability of hemoglobin to carry enough oxygen, thereby worsening the respiratory distress. Hyperinflammatory cytokines such as IL-6, TNF, IL-17A, GM-CSF.G-CSF are found to be associated with vascular injury.

According to the WHO, respiratory infections can be transmitted by respiratory droplets, primarily between people. An analysis of over 75,000 Covid-19 cases in China did not report any airborne transmission of the SARS-CoV-2 virus. These are enveloped viruses, with a positive- sense single-stranded RNA of around 32Kb. The viral particle contains four main structural proteins; the spike proteins, membrane protein, envelope protein and nucleocapsid. The characteristic spike protein, which protrudes from the envelope of the virion, attaches itself to the ubiquitous ACE2 receptor, which appears to be the functional receptor for the SARS-CoV-2. The Virus-receptor interaction, which is a key step in infection and transmission, provides unique intervention possibilities for developing novel drugs, neutralizing vaccines, and immunomodulators. In the absence of a cure, the only choice we have currently, is to follow the best practice public health strategies; social distancing, wearing face coverings, hand washing, tracing infected individuals, and containment of the Covid-19 positive people.

In severe cases, COVID-19 infection seems to initiate inflammation, systemic coagulopathy, acute respiratory failure. The coagulopathy associated with this disease include, increased presence of micro clots in the lungs, high rates of pulmonary embolism, myocardial infarction, ischemic stroke, digital ischemia, renal failure, despite prophylactic anticoagulation. The classical coagulopathy observed in Covid-19 patients, seem to be the result of endothelial dysfunction, followed by endotheliitis. In a large study of 72, 314 Covid-19 patients from China, the authors reported, that those who needed hospitalization had following underlying pre-existing conditions; hypertension, diabetes, and cardiovascular disease [33]. According to a statement by the US Center for Disease Control and Prevention, hospitalization rate during the 4-week period (March 2020) was 4.6%. Therefore, candidates for major treatment and management of coronavirus disease are less than 5% of the Covid-19 positive patients [34]. In these individuals, the intervention will depend primarily on clinical manifestations, diagnosed by the critical care physicians. Several studies have suggested, robust use of antithrombotic and thrombolytic therapies [35]. Because of frequently observed hypoxemia, limited attempts have been made, to prevent hypoxia mediated tissue injury in Covid-19 patients, by providing oxygen therapies [36]. Most recently, researchers from the Royal Free Hospital, and the University College of London, have demonstrated the benefits of iloprost (Prostacyclin; vasodilator) infusion, to improve the ventilation parameters in Covid-19 patients [37].

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