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The Novel Coronavirus Causes Impairment of Blood Vessels and Respiratory System with Head-to-Toe Symptoms and Vaccine Development: An Overview

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Abstract: Blood clotting was reported in April 2020 [1] as another serious symptom due to COVID-19, but also came other reports such as young adults dying due to strokes and heart attacks [2]. The currently known head-to-toe symptoms of COVID-19, seem to indicate vascular as well as respiratory diseases and that 40% of related death are due to cardiovascular complications [2]. In a recently published journal paper in Lancet [3], the authors found that SARS-CoV-2 virus can infect the endothelial cells that line the inside of blood vessels noting that endothelial cells protect the cardiovascular system and release proteins that influence everything from blood clotting to the immune response. In the same paper, the authors showed damage to endothelial cells in the lungs, heart, kidneys, liver, and intestines in patients with Covid-19. Therefore, the emerging belief is that the novel coronavirus is a respiratory illness to begin with, but as it spreads further into blood vessels it becomes a vascular illness that is capable of killing patients via vascular system.

Keywords: Coronavirus, COVID-19, Head-to-toe symptoms, Impairment of respiratory and vascular systems; Vaccine development.

1. How the novel coronavirus spreads and infects the whole body?

As reported previously [4], SARS-CoV-2 enters the body through ACE2 receptors present on the surface of cells that line the respiratory tract in the nose, mouth and throat. Once inside the lungs, the virus appears to move from the alveoli (the air sacs) into the blood vessels, which are also rich in ACE2 receptors. As the virus enters the lung, it destroys the lung tissue and affected people start coughing. The broken blood vessels start infecting the endothelial cells causing a local immune response which inflames the endothelium. It becomes apparent that SARS-CoV-2 is indeed a respiratory virus to start with which then infects the whole body through blood vessels and the circulatory blood cells. The engulfed mucus viruses can also travel from the throat into the stomach and from here it can spread to other organs via digestive system. To be noted is that, the original SARS virus did not spread past the lung and the influenza viruses (e.g. H1N1) also are not known to behave like SARS-CoV-2 virus. Other types of viruses such as Ebola did also damage the endothelial cells, but they are of different kinds that typically infect the lungs.



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The difference between the original SARS and SARS-CoV-2 seems likely to be due to an extra protein which is required by each virus in order to spread, i.e. another protein is needed to crack open each virus so as its genetic material can get into the infected cell. The additional protein that the original SARS virus required is likely to be present only in lung tissue (hence the original SARS was not systemic), but the protein for SARS-CoV-2 to activate and spread is present in all cells, especially endothelial cells [5][6]. It has been reported [6] that SARS-CoV-2 is cleaved by a protein called furin which is present everywhere and this is one of the main differences between the two viruses.

2. Endothelial damage leading to head-to-toe symptoms:

Endothelial cells are known to control the blood coagulation system by secreting/synthesizing thrombomodulin transmembrane protein which is expressed in all kind of tissues except for the microvasculature of the brain. The endothelium prevents thrombosis by providing a smooth surface which prevents the attachment of clotting proteins and other cells, hence blood flows smoothly without getting caught on the blood vessel walls. However, if this smooth surface is disrupted via damaged endothelial cells, inflammation occurs in blood vessels and plaque accumulation causes clot formation leading to cardiovascular disorder and possible heart attacks in patients with Covid-19. Therefore, infection of the blood vessels along with inflammation and endothelial dysfunction do indeed explain many of the known symptoms of the novel coronavirus such as the formation of blood clots, ruptured plaques, heart attacks, strokes, etc.

Blood vessel damage could also explain why people with pre-existing conditions like high blood pressure, high cholesterol, diabetes, and heart disease are at a higher risk for severe complications from a virus that's supposed to just infect the lungs. All of those diseases cause endothelial cell dysfunction, and the additional damage and inflammation in the blood vessels caused by the infection could push them over the edge and cause serious problems.

3. Blood clotting affecting ventilation:

Ventilators are designed to help with moving air rich in oxygen into the lungs, at the same time allowing the exchange of oxygen and carbon dioxide in the blood depending on proper functioning of blood vessels in the lungs. However, if blood circulation is blocked or interrupted due to blood clots in blood vessels, the full benefits of mechanical ventilators will not be achieved and there is clear evidence of blood clots and infection of the endothelial cells within the lungs of patients who died from Covid-19

[7]. This was not the case in patients who died from influenza viruses (e.g. H1N1), who showed nine times fewer blood clots in their lungs [7]. Also, the blood vessel histology is different in the Covid-19 lungs showing the formation of new branches which are likely formed after the original blood vessels were damaged [7]. Blood clots are seen almost everywhere including virus particles within the endothelial cells leading to swelling and the eventual breakdown of the endothelium cell membrane. Therefore, it can be concluded that as the infection of the blood vessels continues, this leads to the spread of the virus through the body infecting other organs leading to head-to-toe symptoms. To be noted is the fact that endothelial cells connect the entire circulatory system with more than 60,000 miles of blood vessels throughout the body, and in this way Covid-19 virus can infect the brain, the heart, and the toe, i.e. the entire human body.

4. The use of drug therapy to stabilize vascular endothelial:

Knowing that Covid-19 is a vascular as well as respiratory disease, there are some existing drugs that may help to reduce the risk of endothelial cell damage. This includes statins which are known to reduce the risk of heart attacks by lowering cholesterol levels and by preventing plaque formation (and stabilization of the existing plaque) leading to reduced rupture of the blood vessels. Also, both statins and ACE inhibitors are well known for their protective role on vascular dysfunction, lowering of high blood pressure, reducing strokes and heart attacks due to their ability to stabilize the endothelial cells. This concept suggests that there might be an alternative drug therapy that stabilizes the vascular endothelial and reduces the risk of infection throughout the human body due to Covid-19.

5. List of health conditions which make us more likely to develop severe COVID-19 symptoms [8]:

COPDs (chronic obstructive pulmonary disease) such as asthma, emphysema and bronchitis; CKD (chronic kidney disease); Liver disease; Serious heart conditions such as coronary artery disease; Type 2 and type 1 diabetes; Sickle cell disease; Obesity (people with BMI>30); Cerebrovascular disease (CVD); High blood pressure; Cystic fibrosis; Pulmonary fibrosis; and thalassemia.

6. Vaccine development:

Vaccine production initially involves pre-clinical testing in laboratory (including animal research) followed up by usually three phases of clinical human trials [9]. In Phase 1 trials, typically very small numbers of people receive the vaccine in order to investigate the safety aspects. Phase 2 trials are larger and evaluate both safety and effectiveness and the vaccine is given to people who have the symptoms similar to those for whom the vaccine is intended. Phase 3 trials are much larger and take longer to complete, during which placebo groups and groups receiving the vaccine are involved for further investigation on how effective the vaccine is and if there are any side effects. Many vaccines also undergo Phase 4 formal with on-going studies after the vaccine is approved and licensed. An initial supply of vaccine will be made available if testing shows a vaccine works well, i.e. millions of vaccine doses will be made before clinical testing is complete which is not unusual and this procedure was followed with the polio vaccine production.

Development and production of all vaccines has involved the use of lab-grown viruses which are either weakened, inactivated, or stripped off their benign parts before being introduced into a healthy and then real patient's body, where they trigger a protective immune response. Therefore, few pharmaceutical companies worldwide in collaboration with higher education institutions are working on such old-school vaccines for Covid-19. However, there are also new leading techniques which are fundamentally different and do not require vaccine developers to grow live viruses such as the coronavirus in cells. One current new technique is that of the messenger RNA (mRNA) platform, also known as the genetic vaccine platform, during which a molecule that helps convert the DNA's blueprint into the functional protein molecule is produced. The mRNA platform works by isolating the virus's particular gene that codes for the protein that the immune system reacts to, hence by printing its genetic sequence, it can be injected into human body. Once injected, our body cells will take up the mRNA and start making the so called spike proteins that trigger a protective immune response. The spike protein allows the coronavirus to attach itself to healthy cells, which is how the virus survives and spreads. Genetic vaccines are therefore designed to expose the immune system to this spike protein (not the virus) so that it will generate antibodies and other immune defence/responses that will block the virus from infecting the body beyond repair. An mRNA Covid-19 vaccine from the drug company Moderna, in collaboration with the USA's National Institutes of Health, is now in Phase II clinical trials. There are currently several other similar genetic vaccines in various stages of development worldwide.

Another new vaccine platform is known as the 'adenovirus platform', which works similar to the genetic vaccines, i.e. it uses human body cells to make proteins that generate an immune response. In these new vaccine platforms, we are infecting people with a known virus with its original genetics replaced with new genetic instructions to make the coronavirus proteins that generate an immune response. So far, Moderna's mRNA vaccine and few adenovirus vaccines have shown promising results in Phase I clinical trials.

7. Vaccines currently in trials at different phases [10]:

Moderna company is developing a two-dose vaccine which is currently in a phase 2 trials with 600 participants, and is scheduled to start phase 3 trial with 30,000 participants in July 2020. It is a messenger RNA vaccine which delivers a message to the human body how to make the antibody that can prevent the infection. If the clinical trials go well, the company aims to make the vaccine available by the end of 2020 or early 2021.

University of Oxford in collaboration with AstraZeneca is developing a single-dose vaccine which contains a modified virus that can trigger the production of antibodies and currently in a phase 2 trial with 500 participants. A phase 3 trial with about 30,000 was planned to start in early summer 2020.

Pfizer in partnership with BioNTech is currently testing four kinds of vaccines in phase 1 or 2 trials in Germany. Their vaccines are also based on the messenger RNA vaccines and each trial will include about 200 people.

Inovio company had already been working on a vaccine for MERS which allowed them to quickly switch to working on a vaccine for SARS-Cov-2. Their vaccine is a DNA vaccine, i.e. a type of vaccine that contains the DNA coding specifically for making the antibodies against SARS-Cov-2 virus, with phase 2 and 3 trials expected to begin this summer in China and South Korea. Inovio believes it can make 1 million doses by the end of 2020.

There are also the on-going phase 1 trials by various other companies such as Johnson & Johnson, Sanofi, Sinovac, CanSino Biologics and a collaboration between the Beijing Institute of Biological Products, the Wuhan Institute of Biological Products and the China National Pharmaceutical Group (Sinopharm).

What can go wrong? There might be some side effects with any established vaccine, which may include soreness of the injection-site and mild rare conditions such as the Guillain-Barre syndrome (GBS), where the body's immune system damages nerve cells, causing muscle weakness and sometimes paralysis. GBS cause is not yet fully understood, but it is known that the syndrome is often the result of an infection with a virus or bacteria. Most GBS affected people will fully recover, but some may develop permanent nerve damage and some vaccines can set it off. Apart from these known side effects, it is also possible that the new vaccine platforms could cause unknown new side effects. More recently, some researchers [11] were really worried about antibody-dependent enhancement (ADE) phenomena where the vaccine can actually make a pathogen more virulent leading to people being continuously re-infected. Such cases are known to be rare and for SARS-CoV-2, it is not clear if any forms of immune enhancement could play a role in infections or vaccines under development and there is no evidence so far. However, Phase II and III clinical trials would identify such risks before the vaccine is widely deployed.

8. Conclusions:

The overall concluding remark is that there is clear evidence of almost full body being affected by SARS-CoV-2 zoonotic coronavirus. For most patients, COVID-19 begins and ends in their lungs, because coronaviruses are respiratory diseases (like the flu). During the SARS and MERS outbreaks, about a quarter of patients had diarrhoea, and this is a much more significant feature of zoonotic coronaviruses. 92% of patients with MERS had at least one manifestation of the coronavirus outside of the lungs. Coronaviruses can affect other systems of the human body, due to the hyperactive immune response and the breakdown of the blood vessels as a result of damage to the endothelial cells via SARS-CoV-2. When a zoonotic coronavirus spreads from the respiratory system, the liver is often one major organ that suffers. Often mild liver injury with SARS, MERS and COVID-19 have been observed and more severe cases have led to severe liver damage and even liver failure. About 6% of SARS patients and almost a quarter of MERS patients suffered acute renal injury and 91.7% of SARS patients with acute renal impairment died [12]. Current studies have confirmed that the novel coronavirus can cause similar renal injuries.

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