# Pathophysiology of COVID-19

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## Introduction:

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV 2) is a virus that has caused the disease, Coronavirus disease 2019. This disease has damaging effects on the respiratory system and in some cases can even impact the cardiovascular system. Although the main origin of the virus is yet to be determined, the structural and genetic similarities point to it being mutated from a common strain, known as the SARS COV, from the mid 2000's.

The virus is a positive single stranded RNA genome that allows it to use the ribosome in host cell to translate the proteins and replicate itself. The symptoms such as shortness of breath and other respiratory problems are caused by the infected alveolar cells in the lung not being able to carry on their normal function as well as the immune system's inflammatory response not allowing normal exchange of carbon dioxide and oxygen between the lungs and the pulmonary vessels.

The damages of the virus did not stop with its physiological impact. The high rate of transmission and lack of treatments and vaccines has had a devastating effect on the global markets and the economies across the globe. The high rate of transmission had left people no choice but self isolation and social distancing to slow down the spread. Since the virus is thought to be originated from China, from the beginning it brought uncertainty to the manufacturing market. Due to China's significant role in the manufacturing and supply chain,

the manufacturing firms and the suppliers saw diminished demand for their products. The virus spreading across the globe at a rapid pace impacted the global economy at rates never seen before. The US stock market along with global securities trade markets dropped at rates which erased the gains that were made in the past four years. The trust in the governments and the institutions had fell and people's lifestyles had majorly changed due to the precautions and fears.

## Structure

In order to develop any treatment and to target a certain virus, the main components to study and map out are the overall structure and how does each organelle of the host cell aid in the mechanism of infection. Just like any other virus, the Novel Coronavirus has four structural proteins that give it the shape, stability and the integrity it needs to carry out its function.

The overall shape and structure of the Novel Coronavirus (SARS-Cov-2) is very similar to the other coronaviruses. To find the overall shape of the virus, the researchers have used electron microscopy. The electron microscope generated images of the infected cells showing spherical particles around the membrane of the infected cells and some being endocytosed into the cell. The virus is known to have a spherical shape with umbrella like spikes (Spike Structural Proteins) protruding from the outer side of the envelope. (Zhang)

The primary and secondary structure of proteins are mainly obtained using the RNA sequence that codes for them. Using the sequence would allow us to map out the amino acid sequence that it would generate. Cross referencing most of the data with SARS and MERS has also allowed them to find the general structure and function of different proteins and organelles. The Viral envelope is a lipid bilayer that holds on the membrane proteins, as well as the integral envelope and spike proteins. The spike proteins make the interaction between the virus and the target

receptor possible. The unique sequence of the spike protein gives the virus an especially high affinity for the receptor. The membrane and the envelope together, encapsulate the interior which contains the nucleocapsid (N protein). The Nucleocapsid proteins, house the genome (RNA sequence) of the virus. We will discuss the function of each protein and organelle in mode detail on the mechanism section.(Tian)

While the structural proteins stabilize the virus and interact with the cells, the nucleotide sequence is the core element of the virus. The RNA sequence of the virus was obtained using DNA sequencing of the patients who have been infected with it.

To find the virus sequence, they took a swab test from a known patient. Next they isolated the virus and cultured the Vero cells to allow the virus to replicate. With the help of the reverse transcriptase, they were able to generate a complementary DNA sequence. The sequence that has been obtained has been the basis for testing people to see whether they are infected.

The virus has a positive single stranded sequence. This feature allows the virus to directly use the host cell's translation machinery such as tRNA, the rough endoplasmic reticulum and the ribosomes to synthesize its amino acid sequence and the proteins and to replicate itself.

About a third of the genome of the SARS cov2 codes for the four structural proteins mentioned above. The remaining two third codes for the enzymes such as RNA polymerase and helicase and other enzymes that aid the virus to replicate itself. (Kindler)

## How Long Can it Last?

The structure and the protein buildup of the virus allows it to remain viable in the air (aerosol droplets) from minutes to hours depending on the temperature, humidity and other conditions.

The virus can also remain viable on different furniture surfaces ranging from hours to days depending on the composition of it.

An experiment to find the aerosol stability of the virus, resulted in new findings. The SARS-COV-2 was transferred to different mediums such as air droplets, copper, plastic and steel. For each environment they used cultured cells that were to be infected upon interacting with this virus. They then measured the resulting titer in 30 minutes intervals to create a dataset. The viral titer refers to the quantity of the virus residing within a liter of collection volume. For this experiment their measurement was $TCID_{50}$ / Liter of air. It measures the concentration of the viral concentration in which half of the cells within that tube have been infected. For example, 1000 TCID50/Liter means that when the virus had concentration of 1000 units in one liter of air in an isolated system, half of the cells in that system were infected. The infection was determined by whether the spike protein of the virus was binding the receptor. (Doremalen)

SARS Cov-2 was viable for several hours following the experiment. In 3 hours, the viral titer went from $10^{4.3}$ to $10^{3.5}$. Although there is a significant drop in that, it indicates that it remains viable in a closed system for many hours to days. The closed system, however, may not be a great predictor of the outside world. People simply do not live in isolated systems. It does, however, show that the virus can still be infectious in public indoor places that are dense in population.

Among the surfaces, the titer had the fastest and sharpest drop on copper. Within 4 hours of application, the viable titrate on copper had reached below the detectable amount. The same concentration of virus applied to cardboard, plastic and stainless steel was viable for much longer. On plastic it was viable almost 72 hours. For steel and cardboard, the viability remained for about 24 hours following the application. (Doremalen)

Another measurement to check for longevity was measuring the half life and the decay rate. The virus decay rate. The decay rate is determined by calculating the rate in which the virus decreases in number of viability. The point in which half of the initial load remains is referred to as the half life. For copper, the half life was 2 hours while for steel and plastic it was 6 hours.

The temperature can also play a role in its viability. In an experiment, the researchers transferred the virus into a droplet culture and applied to different surfaces and a virus transport medium in closed systems. The transport medium was supposed to mimic the conditions in the human body and a normal cell. After the virus was incubated for two weeks, it showed that the virus is highly viable at 4 Degrees Celsius but that changes as temperature increases. The virus was only viable for less than 5 minutes under 70 degrees Celsius. (Doremalen)

## Transmission

The transmission of the virus can be from surfaces in which the virus resides on or the breathing in the aerosol particles that are in the air. To find out how contagious this disease is and how fast it can spread, they used data points tracking people's travel history and the places they have been to which can put them at risk for catching the virus. This would allow them to generate a probability value for an individual to be infected with the virus.

The main measurement for the transmission of virus is the Ro Value. Ro (Reproductive number) refers to the number of cases that can arise from one person having the virus. The data was obtained by aggregating cases that happened in Wuhan, China and tracking the flights and travels. The current accepted value is 2.5 although it has been estimated to be  2.0 to 2.9.

The number indicates that for each individual who has been infected with the virus, can infect on average two other people. There are a few cofounding errors with this methodology. It is almost

logistically impossible to track the movement of every individual and it is even harder to track who did they come in close contact with. Certain jobs requires people to be in close contact with hundreds of people in a day and finding an accurate timeline of every individual is virtually impossible. Another error is that it has been known that the symptoms of this disease can vary and it has a relatively long incubation period. This would make it impossible for anyone to recall who they might have infected or who they have been infected by. The testing is only provided to people with severe symptoms and due to scarcity, they are not readily available to be useful in making any statistical model. (Cascaella)

## Mechanism:

For a cell to be infected by a virus, there has to be a path or a receptor that would give the virus access. SARS Cov-2 is no exception to this rule. In an experiment done to find the main path of the entry of the virus into the cell, first they hypothesized that it would target the Angiotensin Converting.  This hypothesis was made because of the similarity of structure and function of this virus to SARS Cov 1. To test the hypothesis, they separated and cultured a group of 293T cells. For the control group, they modified the RNA sequence of some cells to take out the ACE-2. Applying the virus to different groups of cells, showed that the cells that did not express any ACE receptor were not infected by the virus. They further confirmed that the virus' Spike (S) protein has a higher affinity for the ACE2 receptors than its predecessor (SARS cov 1) did. The S protein on the outside of the envelope binds to the target receptor of the cell.

First the S protein of the virus binds to the ACE2 receptor on the membrane of the cell. This allows a conformational change that allows the virus to then fuse with the membrane and endocytose into the cell cytoplasm. (Cascella)

The genome in the virus is positive single stranded. This allows the genome to be released and use the ribosome of the host cell to create the polymerase enzyme. The polymerase enzyme then helps with the replication of the viral genome. The rest of the genome also codes for the structural proteins of the virus. They use the rough endoplasmic reticulum and the ribosomes to synthesize the structural proteins. The newly created nucleocapsid then houses the genome and the rest of the structural proteins get assembled and a new mature virion is now created. The new virus now gets exocytosed outside of the cell. (Cascella)

## Respiratory System and Immune System:

The SARS Cov-2 most severely affects the respiratory system. The virus floating in air droplets and people inhaling the contaminated droplets, makes the respiratory tissues the most attractive destination for the virus to gain entry. As they find themselves in deeper sections of the respiratory system, such as bronchioles and alveoli, they bind to the receptors on the surface of the cells lining them.

When the virus infects the cells lining the alveoli, the cell releases cytokines into the bloodstream. The inflammation then causes the blood vessel lining to become more permeable and allow the fluid from the capillaries to spill out into the alveoli and its surroundings. This would then disrupt the surfactant cells in the alveoli. The surfactants not being able to carry on their functions, would increase the surface tension on the alveolar cells and may ultimately cause it to collapse and not be able to exchange gas required for respiration effectively. This sequence of events causes shortness of breath caused by the virus. (Tian)

Neutrophils are also recruited by the immune system as a result of the inflammation. Neutrophils then release reactive oxygen species and proteases with the aim of destroying the

virus. Unfortunately, this reaction has its own collateral damage. The proteases will destroy the virus but they can also damage structure and integrity of the alveoli cells. This causes further problems with breathing. Lowering the partial pressure of Oxygen would lead tohyperventilation. The hyperventilation, without the adequate alveolar cells to perform the gas exchange causes most of the symptoms associated with it such as difficulty breathing. (Tian)

In some severe cases, the immune response can impact beyond the respiratory system. The inflammation would cause the dilation of blood vessels and increase its permeability. Lower blood volume in wider vessels would ultimately cause lower blood pressure.

## Testing

So far there are two approved testing methods that are being widely used: RT-PCR and Serological.

The Real Time Polymerase chain reaction test is most commonly used . In this method, they first take a swab from either the tongue or throat of the patient. Next they isolate the mRNA from the sample cell. Then using the enzyme reverse transcriptase, they obtain a complementary DNA sequence. Then they amplify certain regions on the sequence to then test the sample collected against the genomic sample of the virus. If the Viral RNA and the obtained cDNA bind, it means that the viral sequence were in the cells and the patient has in fact been infected with the virus. The binding would show a darker tag (  on the experiment result.

The newer method of testing involved testing to see if the patient has the antibodies specific to the virus. The B cells in the immune system get activated upon finding a foreign invader. The B cell, now called plasma cell, would produce antibodies that would mark the invader for destruction. Upon exposure to an unknown invader, the B cells mature and make the antibodies.

The memory B cells then mature to fight that specific invader. Upon exposure of the pathogen to the memory B cells, they will employ a faster and heavier immunity response.

The Antibody testing employs the ELISA method. In this test, they get a sample of the blood of the patient and use the antigens specific to the virus to see whether they have the Memory B cell needed to fight against that. If the antigen interacts with the memory B cells, it would mean the person must have had prior exposure to the virus and has built immunity against it. This mainly confirms a past exposure as opposed to a current infection.

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