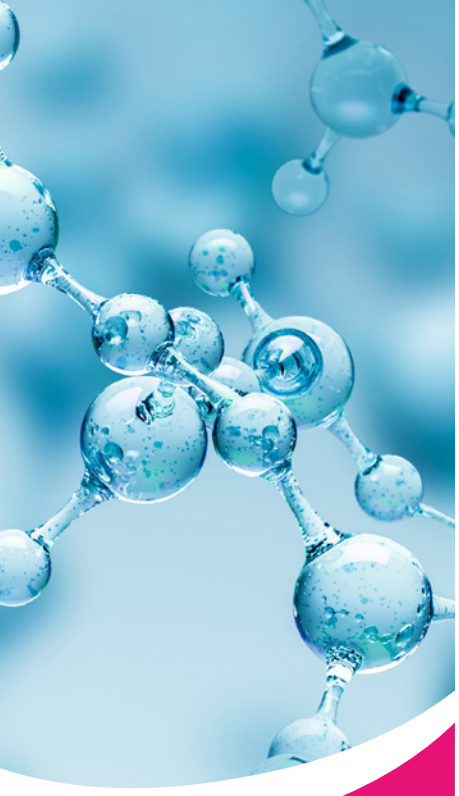

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Nitric Oxide & Immunity

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More than 99% of Italy's coronavirus fatalities from COVID-19 were people who suffered from previous medical conditions. More than 75% had high blood pressure, 35% had diabetes, and 33% had heart disease . All of these conditions are indicative of nitric oxide (NO) deficiency.

Severe Acute Respiratory Syndrome (SARS) risk complications are highest in those with hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer.

NO has been shown to be extremely effective antiviral against the SARS-CoV.

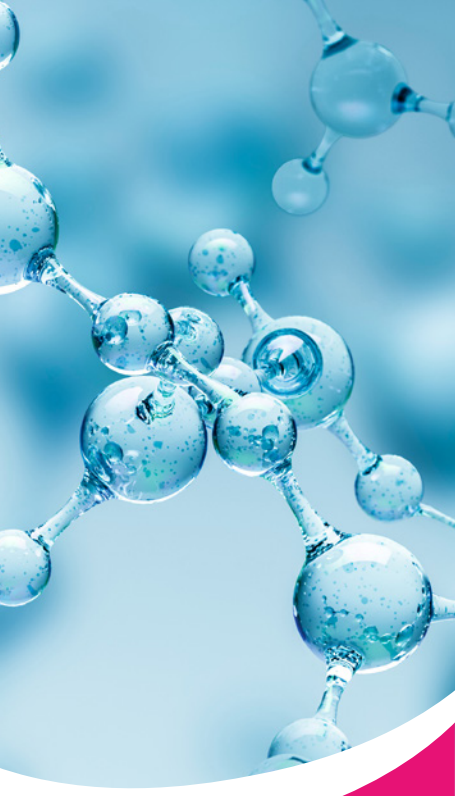
What are the physiological processes?

NO dysregulation, oxidative stress, and hypoxia are a central cause of dysfunction in CVD, diabetes, hypertension, respiratory diseases and cancer.

- **NO Dysregulation:** The L-arginine pathway requires coupled nitric oxide synthase (NOS) enzyme to produce NO. Depleted BH4 levels can cause NOS to become uncoupled and produce superoxide from L-arginine rather than NO. If NOS is uncoupled, the body will be unable to upregulate NO production to tackle hypoxia and oxidative stress[4].
- **Oxidative stress** increases exponentially in critically ill patients. Supporting nitric oxide production not only decreases the production of superoxide, it scavenges Reactive Oxygen Species (ROS) to decrease oxidative stress.
- **Hypoxia** causes an increase in NO production through the nitric oxide synthase (NOS) enzyme and stimulates nitrite reductases to increase the production of NO. NO opens up the circulation and microcirculation to increase oxygen delivery to cells.
    - In fact, NO is required for oxygen delivery from the red blood cell (RBC) to the cells. Hypoxia Inducible Factor (HIF-1a) triggers increased expression of furins which leads to cleavage and activation of CoVID-19. Cells replete with oxygen decrease, deactivate and degrade HIF-1a which decreases furin enzymes.

Clinical Data:

- **2004** – use of nitric oxide (NO) in patients suffering from SARS-CoV, reversed pulmonary hypertension, improved severe hypoxia and decreased duration of ventilation support.
- **2005** – endogenous production of NO stopped the SARS-CoV viral replication process. In fact, an 82% decrease in viral replication was observed[2].
- **2020** – NO gas inhalation for SARS-CoV study undertaken[3].



"Well-vascularized tissues are more resistant to infections and capable of localizing/containing offending agents. By contrast, poorly vascularized tissues are relatively inefficient in responding to inflammatory stimuli."

– Robbins Pathology.

"This means that if you have good circulation and blood flow to every tissue in the body, then this allows your immune system to mobilize a strong defense against any invading pathogen. If you don't have good blood flow and circulation, the infection takes hold and makes you sick and can sometimes kill you. This is basic physiology. The regulation of blood flow and circulation is based on your ability to produce nitric oxide[9]."

– Nathan S. Bryan, Ph.D

ACE 2: SARS-CoV 2, which causes COVID-19, binds and enters human cells via the Angiotensin Converting Enzyme 2 (ACE2). There are ACE2 receptors on epithelial cells of the lung, intestine, kidney and blood vessels. ACE2 is responsible for the degradation of Angiotensin II (Ang II).

Ang II stimulates NADPH oxidase (NOX) to increase the production of superoxide as well as the production of cytokines, specifically Interleukins IL 6. IL 6 and other cytokines, such as IL 1B and IL 18, increase the severity of CoVID-19. Increased IL 6 and ferritin is closely associated with fatality.

There is some controversy around the discontinuation of Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin II Receptor Blocker (ARB) medications that are used in the treatment of hypertension and diabetes. ACEI and ARB can upregulate ACE2 receptor expression on the epithelial cell linings.

The American College of Cardiology and the American Heart Association stated "there are no experimental or clinical data demonstrating beneficial or adverse outcomes among CoVID patients using ACEI or ARB". This is where Physician judgement needs to be used on a case by case basis[5].

NLRP3 Inflammasomes like IL 1B and IL 18 sense pathogens and danger. They are key to development of Acute Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI).

IL 1B initiates hypoxia leading to ARDS and induction of cytokine storms. Melatonin and NO have been shown to suppress NLRP3 inflammasome activation. NO prevents IL 1B and IL 18 release by macrophages[6,7].

mTOR regulates cell growth and cell proliferation. Viruses, however, can use mTOR as a host cell for replication[8].

Substances that stimulate mTOR include glutamine, arginine, leucine, methionine, glucose, insulin, excess folate, iron, pesticides and cytokines. For example, cautious use of bone broths, protein drinks, dairy, and plastics with the potential for xenoestrogen activity are to be taken into consideration. Ang II stimulates NOX as well and mTOR.

Autophagy is an essential counterbalance to mTOR and is often described as the "clean-up crew". Caloric restriction, fasting, resveratrol and turmeric stimulate autophagy. Supporting the function of SIRT 1,2 and 3 also enhances autophagy.

Some mTOR inhibitors have been shown to have antiviral actions. An example of these are Rapamycin and Rapalogs.

Considerations:

- **Increased vegetable intake** for their fiber, phytonutrients, antioxidants and **dietary nitrate concentrations.**
- **Limit sugar intake,** as it impairs the immune response and impacts the function of the White Blood Cells (WBC).
- **Vitamin C** intake increases Natural Killer (NK) cells, which are especially responsive to viruses. It also supports optimal functioning of T and B cells. These are the immune cells involved in memory and antibody production.
    - NO production requires BH4 (rate limiting step). Ascorbate is the only molecule that can take BH3 into BH4. If BH3 cannot be recycled to BH4, it is oxidized to BH2. BH2 will Uncouple NOS, increase superoxide, increasing oxidative stress[10].
- **Minimize stress and ensure optimal rest.** Stress, and its resulting increased cortisol release, impairs the immune response and nitric oxide production by inhibiting NOS. Long-term chronic stress increases inflammation and dysregulates the immune response. When one is sleep-deprived, there is an increase in inflammatory markers and increased susceptibility to illness.
- **Decreasing toxin exposure** will help minimize oxidative stress. Examples of these include environmental pollution, heavy metals and pesticides.
- **Maintaining a regular exercise habit** as it supports the production of NO.
- **Melatonin** inhibits NLRP3 activation, decreasing inflammasome release of IL 1B ad IL[11].
- **Nitric oxide** prevents IL 1B and IL 18 release from macrophages decreasing the possibility of cytokine storm.

Supporting the nitrate to nitrite to NO pathway not only increases the production of NO directly, but it also helps recouple NOS to decrease the production of superoxide and increase NO through that pathway.

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