

I. COVID-19 and Post-COVID-19 Sequelae:

The novel coronavirus has caused a significant pandemic throughout the world. Human suffering, morbidity and mortality are rising every day. There is no completely effective drug treatment for the virus once it is contracted. COVID-19 causes a clinical course which can range from mild symptoms to severe multi-organ failure and death. It is believed that the later is caused by the precipitation of a serum cytokine storm (due to high levels of interleukin tumor necrosis factors) being released. There is a transcriptional factor known as nuclear factor Kappa B (NF-kB) which may promote the production of these inflammatory cytokines.

It is believed that a well-balanced autonomic nervous system may be protective in patients who are infected the novel coronavirus. Specifically, an adequately functioning vagal or cholinergic nervous system acts via an anti-inflammatory mechanism in preventing the cascade of overproduction of pro-inflammatory cytokines. It is also postulated that when this vagal-driven pathway is deficient, cytokine storm may become rampant. In addition, it has been postulated that an imbalance of the sympathetic nervous system with over-expression can be quite harmful, especially in patients who are hypertensive or diabetic and have heart disease. An overactive sympathetic nervous system can promote cardiopulmonary dysfunction and electrical arrhythmias, some of which may be lethal. This in conjunction with a deficient parasympathetic nervous system, which may promote cytokine storm can lead to devastating effects of the coronavirus on various organs in the body.

For prophylaxis, we and others have empirically given antioxidants in high doses. Also, anti-inflammatories such as fish oil have been used. However, the precise cocktail that is most protective has yet to be elucidated.

COVID-19 causes an inflammation response. It affects the autonomic tone adversely and presents with a hypercoagulable state promoting the production of blood clots which may cause lower extremity thrombosis, pulmonary emboli, myocardial infarctions (heart attacks), and even strokes. It is believed that the angiotensin converting enzyme-2 receptor is down-regulated and participates in

this response. Excess catecholamines are increased and myocardial injury is commonly seen and is measured by the blood test known as high-sensitive troponin, which are often elevated in a high percentage of patients who are affected the with COVID-19 virus. In addition, hypoxemia, that is the lowering of oxygen in the blood, also contributes to organ damage.

An example of a disease entity that chronically causes damage to the autonomic nervous system is diabetes. Diabetics have a loss of or damage to myelinated vagus (parasympathetic) nerve axons. It is believed that poor blood glucose control accelerates this damage to the parasympathetic or vagus nerve. Viral infections such as Covid can rapidly damage or cause malfunction to the vagus autonomic nervous system. Since the vagus autonomic nervous system is most important in immune protection and anti-inflammatory protection diminishing or improving the nerve fibers which carry these impulses and cause more rampant diseases once a virus has infected the human body.

While there is no doubt genetic differences between individuals who have a proper autonomic balance between the sympathetic and parasympathetic systems in the way they react to certain viruses such as COVID-19, we are not able to identify what these markers are. Unfortunately, the genetic predisposing factors have not been identified. Comorbidities, such as hypertension, diabetes, obesity, advanced age, kidney disease, liver disease, and lung and cardiac disease predispose to COVID-19 adverse effects and protracted courses.

Some investigators have suggested that vagal nerve stimulation may be protective and support good cholinergic or vagal tone especially during infection or after infection.

Post COVID-19 syndrome is a grab bag term. Some have termed this the "Long Covid Syndrome." After any significant viral infections, some individuals recover completely, and others are left with chronic fatigue and exercise intolerance. This has been seen with the Epstein-Barr virus, and at one time it was thought that this was the sole contributor to chronic fatigue syndromes. However, many viruses

have been shown to be responsible to promote oxidative stress and adversely affect the cells at the mitochondrial level and cause abnormal mitochondrial function and energy production. Epstein-Barr, herpes virus, hepatitis virus, coronavirus, and many others are potential culprits. Therefore, it is no unique to the COVID-19 infection that chronic fatigue and recovery abnormalities ensue.

We believe most causes of post-viral chronic fatigue are due to orthostatic intolerance. Individuals are not able to stand up for prolonged periods of time or function without getting extremely tired with minimal exertion. This is due to venous pooling of blood in the lower extremities and due to failure of the sympathetic nervous system to adequately respond when an individual stands. If there is not a proper venous return to the heart, the stroke volume lessens, and the heart rate can race in an attempt to compensate for the lower cardiac output. This causes accelerations of the heart rate with standing and produces a postural orthostatic tachycardia syndrome or POTS syndrome. Older patients are often affected in a different way. They may drop their blood pressure more than 20 points on standing and develop an orthostatic hypotension response. This can cause dizziness and even syncope or fainting. The symptoms are probably a result of decreased cerebral perfusion or decreased autoregulation to the brain especially in the standing position or when one is walking or exerting themselves. Brain fog and cognitive dysfunction are often reported with these post-viral syndromes, and it is being seen more commonly now with COVID-19 (long syndromes). Patients have difficulty in word finding, short-term memory, reading sentences and absorbing what they have read, and focusing on simple tasks. Balance and vestibular problems, visual problems and hearing problems are common especially when standing. This contributes to the so-called orthostatic intolerance symptoms.

Disruption of the autonomic nervous system can cause anxiety and depression. Lack of blood supply to the upper extremities can cause "coat hanger pain" when standing due to abnormal function of the sympathetic nervous system (the sympathetics are the accelerator of the body and if they malfunction when one stands, venous return is not complete to the heart and, hence to the brain). Patients with orthostatic intolerance will often need an integrated holistic approach including compression stockings and compression garments. This

includes: (1) volume expansion measures including fluids with electrolytes and pharmacologic agents which increase intravascular volume (agents such as fludrocortisone or desmopressin) and (2) vasoconstrictors which replace the sympathetic withdrawal which is not operating when one stands (agents such as midodrine and Northera). Please review this paragraph for accuracy.

Digestive system issues may also develop due to an autonomic imbalance and produce irritable bowel syndrome flare-ups, gastroparesis, many digestive difficulties and gastroesophageal reflux disease and anorexia, Sleep disturbances and headaches often can occur. Chest pains and shortness of breath and exercise intolerance are common symptoms when orthostatic intolerance due to lack of venous return from the lower extremities fails to deliver blood to the heart and brain. This lack of venous return causes a decrease in stroke volume from the heart and a lower cardiac output. A compensatory sinus tachycardia may occur and the heart rates at times can go over 120 beats per minute. We see this with postural orthostatic tachycardia.

More serious problems seen in post-Covid syndromes results from myocardial damage which occurred during the active infection and from lung damage which occurred during the active infection. In these instances, chest pains and dyspnea may be the result of structural abnormalities in the heart and lungs and not symptoms from orthostatic intolerance issues. This a more serious problem and requires noninvasive cardiac testing, such as stress test, echocardiography, ambulatory monitoring, and perhaps more sophisticated imaging techniques as required clinically. Also, comprehensive pulmonary function tests and pulmonary imaging may be required.