Review Article

Anticipating the Challenging and Unpredictable Long Term Cardiovascular Effects of COVID-19: A Review

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Introduction:
SARS-CoV2 infection can impact all organs structurally and functionally. Persisting symptoms in patients recovering from coronavirus disease 2019 (COVID-19) are common and with close follow-up can be detected in nearly 90% of patients 60 days from the original diagnosis¹. The most common symptoms are fatigue, dyspnea, joint pain, chest pain, cough, insomnia and headache. Given the well-documented involvement of the circulatory system in COVID-19, including small, moderate and large-sized veins and arteries, coupled with robust immune and resulting local and systemic inflammatory responses, one would anticipate a prolonged recovery period and potentially long-term cardiovascular effects. The following review summarizes the pathogenesis of structural, functional and metabolic abnormalities associated with COVID-19 and postulates long-term cardiovascular effects and management strategies under a broad clinical umbrella referred to as post-COVID-19 syndrome.

Acute stages of COVID-19: setting the stage for prolonged clinical effects
The frequency of cardiac injury, vascular dysfunction and thrombosis in patients with COVID-19, including those persons with either no or minimal symptoms during their initial infection, raises important questions about potential long-term cardiovascular effects: these could include heart failure, life-threatening arrhythmias, sudden cardiac death, impaired myocardial flow reserve from microvascular injury, coronary artery and aorta aneurysm formation, hypertension, labile heart rate and blood pressure responses to activity, accelerated atherosclerosis and both venous and arterial thromboembolic disease². Indeed, events during the acute phase of disease, including those that are clinically unsuspected and undiagnosed³ will increase the risk for recurring events⁴. How will the medical community follow patients with COVID-19? How will future events be prevented?

The COVID-19 pandemic and its reporting has focused primarily on two areas—the number of cases and the number of deaths. Both statistics are of great importance, yet neither sufficiently captures an equally important metric of morbidity that is responsible for resource utilization, assessment of vulnerable populations, cost, recovery, long-term health effects, and quality of life⁵. A morbidity index of COVID-19 survivors is particularly relevant when

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considering co-morbid factors and traits for SARS-CoV-2 infection susceptibility, need for hospitalization, level of care and their collective impact on the severity of illness.

Acute cardiac injury:
Myocardial Infarction stemming from supply–demand mismatch (Type 2) is common in clinical practice and considered to be ischemic in etiology\(^6\). Patients with COVID-19 can experience hypoxia, hypotension and distributive shock with resulting myocardial injury diagnosed by serial cardiac troponin assays with quantitative values > 99th percentile of the upper reference limit determined in a normal reference population. In addition, COVID-19-associated coagulopathy and hyperinflammation syndrome can cause micro and macro-myocardial injury of non-ischemic etiology\(^7\).

Type 2 myocardial infarction is associated with one-year mortality rates of 10–25% owing to co-morbid conditions and underlying atherosclerotic cardiovascular disease. Similar mortality rates have been reported following non-ischemic myocardial injury. In COVID-19, small vessel inflammation, injury and dysfunction contribute to myocyte damage, as does pericyte injury and impaired myocardial perfusion\(^7\).

Early reports of COVID-19 identified a high proportion of hospitalized patients with reduced left ventricular ejection fraction. Indeed, in one series 35% of patients had an ejection fraction less than 50% and features of stress-induced cardiomyopathy were identified in a number of patients\(^6\). Patients with COVID-19-associated myocardial injury likely remain at risk for cardiovascular events following hospital discharge. The duration of risk, optimal surveillance and management strategies are under investigation and must be clearly defined.

Viral myocarditis:
Myocarditis occurs in a wide range of acute viral infections, including adenovirus, Human Immunodeficiency Virus (HIV), Epstein-Barr Virus, and Influenza virus to name a few. Observational data, coupled with virologic and molecular diagnostic studies suggest that enteroviruses, including coxsackievirus, parvovirus and adenovirus are among the most common causes of myocarditis.

Animal models of enterovirus-induced myocarditis demonstrate RNA detection in the acute phase and chronic phase of dilated cardiomyopathy. In a murine model of coxsackievirus \(^3\)-myocarditis, features of acute infection including rapid progression of myocardial lesions, infected myocytes and inflammatory cells is followed by a persistent pattern with reduced inflammation and a slow progression of myocardial lesions. Infection is often restricted to atrophic myocytes and fibroblasts\(^9\).

While the virus itself is cytoxic causing myocyte injury, a majority of cases of severe myocarditis and subsequent post-viral cardiomyopathy are governed by a maladaptive or overly robust inflammatory response to viral antigens\(^10\). Many viruses associated with myocarditis infect the heart secondarily following an initial infection in the lungs or gastrointestinal tract. By contrast, some viruses are highly cardiotropic. For example, parvovirus \(^19\) can infect the endothelial cells of venules, capillaries and arterioles\(^11\). Cytokine activation follows, causing apoptosis of endothelial cells, endothelial dysfunction and marked lymphocyte accumulation within the microvasculature. Myocyte injury is the result of perfusion abnormalities rather than direct myocyte viral entry and damage. Myocarditis following a viral infection is viewed under the pathophysiology-based lens of autoinflammatory disease\(^12\).

SARS-CoV-2-associated myocarditis:
Given the duration of viral shedding in SARS-CoV-2 infection and COVID-19, as well as the relatively high density of ACE2 receptors expressed in cardiomyocytes, one might anticipate cases of myocarditis and myopericarditis. Lindner and colleagues performed autopsies on 39 decedents (median age 85 years) with COVID-19. Cardiac tissue contained SARS-CoV-2 in 24 decedents (61.5%). Viral loads above 1000 copies per \(\mu\)g RNA were documented in 16 cases (41.0%). Proinflammatory gene upregulation was present in each decedent with high viral loads\(^13\). A prospective observational cohort study of 100 adult patients with severe COVID-19 and subsequent recovery compared to age- and sex-matched healthy volunteers and risk
factor-matched patients was conducted by Puntmann and colleagues. The median time from diagnosis and cardiac MRI was 71 (64–92) days. At the time of cMRI, high-sensitivity (hs) troponin was detectable in 75% of patients, NT pro-BNP (brain natriuretic polypeptide) was normal. Compared with the control groups, patients recovered from COVID-19 had lower left ventricular ejection fraction, higher left ventricular volumes, higher left ventricular mass and raised T1 and T2 weighted images. The overall finding suggests that approximately half will have recovery over the next 6–12 months, 25% will experience chronic systolic dysfunction and 25% will worsen and require advanced mechanical therapies or heart transplantation. The long-term effects of SARS-CoV-2-associated myocarditis are not known, but as summarized above for viral myocarditis could include heart failure, impaired exercise tolerance, atrial tachyarrhythmias, ventricular tachyarrhythmias, bradyarrhythmias and sudden cardiac death. Subclinical myocarditis may portend a particularly high risk for sudden death during moderate-to-high intensity physical activity, raising concern and a cautionary note in the athletic community. The vascular pathology of COVID-19 is a topic of great interest. As previously described, necropsy and post-mortem biopsies of decedents with COVID-19 have consistently shown endotheliitis and accompanying macro and microvascular thrombosis within arteries, veins, arterioles, capillaries and venules in all major organs. Endothelial cells produce microvesicles in response to inflammatory conditions and inflammatory mediators, including cytokines, thrombin and complement 5a. In turn, microvesicles impair vascular integrity, gap junctions, promote neutrophil binding, release NETs and facilitate tissue-level inflammation. The wide-spread vasculitis described in patients with COVID-19 likely contributes to thrombosis, hemodynamic instability and autonomic dysregulation. The question being raised is, "how long will the vascular injury persist and at what cost to a full and functional recovery?" Baroreceptor dysfunction: The diffuse endotheliitis and vascular injury observed among patients with COVID-19 may have lasting hemodynamic and autonomic regulatory effects. The arterial baroreceptor system is intimately involved on a moment-to-moment basis with maintaining vascular tone and blood pressure homeostasis. For example, arterial baroreceptors (stretch receptors located in the carotid sinuses and aortic arch) provide continuous feedback on blood pressure to the central nervous system, which responds with physiological efferent autonomic activity. Activation of arterial baroreceptors in response to increased blood pressure causes activation of vagal cardio–inhibitory neurons and a decrease of sympathetic neuron discharges to the heart and peripheral resistance bed. The end-result is a decrease in heart rate, cardiac contractility, peripheral vascular resistance and venous return. By contrast, a decrease in sympathetic activity and vagal inhibition, leads to tachycardia and heightened cardiac contractility, vascular resistance and venous return. Any changes to this finely tuned mechanism can cause impaired blood pressure and heart rate responses to a change in posture, sleep and other resting states and physical activity. COVID-19-associated dysautonomia could be one of several manifestations of diffuse vascular injury. Molecular and cellular adaptation, maladaptation and reset states: Potential role in recovery following COVID-19 The early stages of COVID-19 are driven by a rapidly replicating virus and its direct effects on host cells. The transition stage of disease is less about the virus itself and more aligned with host responses, particularly unregulated immune and inflammatory system activation. SARS-CoV-2 tolerance is an attractive construct because its primary goals are to limit maladaptive response, attenuate tissue/organ damage, preserve physiological function and initiate recovery. By contrast, these same mechanisms if poorly regulated either because of comorbid illness or the virus itself may contribute to long-term pathological effects.
Immune mechanisms:
The variability of symptoms experienced by persons with COVID-19 is one of many areas of investigation. Braun et al. investigated SARS-CoV-2 spike protein reactive CD4+ T cells in patients with COVID-19 and SARS-CoV-2 unexposed healthy donors. Peripheral blood SARS-CoV-2 S-reactive CD4+ T cells were detected in 83% and 35% of samples, respectively. Among healthy donors the S-reactive CD4+ T cells reacted primarily to C-terminal S epitopes that displayed homology to spike glycoproteins of human endemic coronaviruses. S-reactive T cell lines cross-reacted to SARS-CoV-2 C-terminal S protein epitopes. The impact of S-cross-reactive T cells on vaccine response will be an important area of investigation.

SARS-CoV-2 disrupts normal immune responses, leading to both an impaired immune system and, in some cases, an uncontrolled inflammatory response. Under ideal conditions, treatment(s) would be designed to enhance viral immunity and attenuate systemic inflammation. Immune patterns are associated with disease progression and severity in patients with COVID-19. The patterns described to date are as follows: lymphopenia, reduced CD4+ T, CD8+ T, memory helper T cells, natural killer cells and B cells, T cell activation with expression of CD69, CD38, CD44, OX40, IL-2, TNF-±, and IFN-³, T-cell and natural killer T cell exhaustion, decreased basophils, eosinophils and monocytes, increased production of cytokines and increased IgG and total antibodies.

Patients experiencing moderate or severe COVID-19 have pulmonary epithelial cells with a three-fold increased expression of ACE2 receptors compared to healthy controls.

The association between viral infections and long-term metabolic abnormalities is recognized. Wang summarized the recovery pathway among patients with severe acute respiratory syndrome (SARS)—a global epidemic that emerged in 2003. Lung performance did not return to normal for 6–12 months following. Six min walk distance improved in the first 6 months of recovery, however, it did not reach normal values and physical activity-related quality of life scores were much lower than normal populations even at 1-year. The findings suggest that muscle weakness can persist for a prolonged period after a severe respiratory infection. As with other serious illnesses, neurocognitive impairment (memory, recall, attention and concentration) and physiologic effects (depression, post-traumatic stress) can persist for months to years. While pre-existing conditions contributed, in many instances the acute respiratory illness accompanied by sympathetic activation, altered cerebral microvascular integrity, changes in intracranial pressure, systemic inflammation-associated blood–brain barrier dysfunction and cytokine-mediated hippocampal damage was believed to be primarily responsible.

Fig.-2: The disease phases of patients with COVID-19
Lipid mechanisms:
The risk for COVID-19 on a high-spectrum of severity is heightened by metabolic and lipid-related comorbid factors. Because lipids play an important role in regulation of immunity, changes in lipidomic profiles could have both near-term and long-term consequences.

Vascular mechanisms:
Ackerman and colleagues performed a detailed necropsy-based analysis of COVID-19 decedents. In all cases there was diffuse alveolar damage with necrosis of alveolar lining cells, Type 2 pneumocyte hyperplasia and linear intra-alveolar fibrin deposition. A multiplexed analysis identified 79 inflammation-related genes that were differentially expressed compared to influenza H1N1 decedents. Fibrin thrombi of the alveolar capillaries were identified in all cases. In two cases, there were thrombi in precapillary, capillary and post-capillary vessels. Employing a three-dimensional micro-CT of pulmonary specimens, nearly total occlusion of precapillary and postcapillary vessels were observed. The extent of endothelial cell inflammation and thrombosis was associated with structurally deformed capillaries and microvascular corrosion casting. Intussusceptive angiogenesis (nonsprouting angiogenesis) occurred along with endothelial cell disruption of gap junctions and loss of contact with the basal membrane.

The extent of alveolar damage, architectural changes and vascular disruption observed in severe cases of COVID-19 are likely to cause prolonged or life-long functional abnormalities with attendant physiological limitations.

Clinical follow-up strategies:
The frequency of cardiac injury, vascular dysfunction and thrombosis in patients with COVID-19, including persons with either no or minimal symptoms during their initial infection, raises important questions about potential long-term cardiovascular effects. A proactive approach to care following hospital discharge and among patients with persisting or new symptoms with a goal of prevention, education and communication is needed.

The purpose of establishing a COVID-19 Cardiovascular Clinic is to

1) proactively evaluate patients who have contracted SARS-CoV-2 infection,
2) identify cardiovascular abnormalities that could portend future serious or life-threatening events, and
3) establish a foundation for optimal management and follow-up.

Patients with laboratory-confirmed SARS-CoV-2 infection are the focus of the clinic. Those requiring hospitalization, an intensive care unit stay and in whom there was documented cardiac injury (elevated troponin), heart failure, arrhythmias or vascular inflammation (skin or other organ biopsy) will be prioritized for evaluation. An appointment in the COVID-19 Cardiovascular Clinic could be made at the time of hospital or rehabilitation facility discharge. Persons who test positive for Covid-19 who are initially asymptomatic, but then develop shortness of breath, impaired exercise tolerance, declining stamina, persisting fatigue, presyncope or syncope should also be evaluated. Delayed-onset clinical events among SARS-CoV-2 positive persons without initial symptoms, based on prior experience with viruses, will require documentation in medical records, careful history taking and reporting.

Testing and diagnostic platforms:
Patients will have a complete physical examination performed by an experienced clinician. A carefully selected battery of laboratory should be considered (Table1). A carefully selected menu of diagnostic studies to determine the status of cardiac and vascular health could also be performed as clinically indicated (Table2). Patients would receive a COVID-19 Cardiovascular report that summarizes the findings of each recommended test, instructions for a follow-up visit or referral to a specialty clinic or treatment as indicated according to the best available evidence. An existing electronic health record or secured dedicated database should be used for documentation.

Table-I

| Covid-19 cardiovascular clinic blood and urine tests |
|-----------------------------------------------------|
| C-reactive protein (CRP)                             |
| d-dimer                                             |
| Von Willebrand Factor (VWF): antigen and activity   |
| Interleukin (IL)-6                                   |
| Complete blood count with differential              |
| Basic metabolic profile                              |
| Urinalysis (protein, active sediment)               |
| Anticardiolipin antibody screen                     |
| Ferritin                                            |

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**Table II**

*Covid-19 cardiovascular clinic diagnostic menu*

- ECG
- Echocardiogram (with strain calculation)
- PET-CT (option if elevated troponin during hospitalization)
- Cardiac MRI (preferred for evaluation of suspected myocarditis)
- 24 h Holter Monitor (If elevated troponin or arrhythmias during hospitalization or a left ventricular ejection fraction <40%)
- Pulse wave velocity test
- Brachial reactivity test
- Heart rate variability test
- Venous duplex scan
- Pulmonary CT angiography

**Expertise and team-based approaches:**

Establishing a COVID-19 Clinic, by the very nature of SARS-CoV-2 infection and its widespread target organ involvement, will require a collaborative and multidisciplinary team of experts. One would anticipate a need for representation from the following specialty and subspecialty groups: cardiology (electrophysiology and heart failure), vascular medicine, pulmonary medicine, nephrology, neurology and infectious disease. Access to expertise in hematology, dermatology, psychiatry, immunology, rheumatology and social services will be a requirement as well.

COVID-19 clinics represent a means to render a continuum of care for patients, but they can also serve as an underpinning for research, including long-term cohort studies and research network development. The natural history of COVID-19 and the many likely forms of post-COVID-19 syndrome can only be understood by establishing initiatives for follow-up, appropriately configured databases, careful documentation with quality controls, audits, experienced staffing, over-sight and sufficient funding.

Understanding the cardiovascular response to SARS-CoV-2 re-infection and Influenza infection will be a particularly important area of research given the common theme in cardiovascular diseases, disorders and conditions of a "second hit phenomenon" that can accelerate pathological abnormalities and lead to clinical events. The bar must be set high to assure that research undertakings meet the vigorous standard needed to inform and advance the field.

**Concluding thoughts and future directions:**

SARS-COV-2 infection is characterized by its protean nature and rapidly evolving understanding of its acute, immunological, hematological, dermatological, psychiatric, infectiological, rheumatological, immunological, and social sciences. It is imperative to establish a multidisciplinary team of experts to provide a comprehensive approach to the diagnosis and management of patients with COVID-19 syndrome.

*Fig.-3: COVID-19 clinics for the diagnosis and management of patients with post-COVID-19 syndrome.*
subacute and, in all likelihood, chronic cardiovascular effects. Securing an initial diagnosis and documenting early signs, symptoms, diagnostic studies and complications, followed by an ambulatory clinic or office visit for “recovered” patients will be a vital step toward understanding COVID-19 and its comprehensive management. Research platforms must be established to translate new knowledge of post-COVID-19 syndrome to optimal patient care.

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