Coronavirus Disease-19 (COVID-19) and Heart Failure: Current Perspective

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Abstract
COVID-19 has been the biggest pandemic which the world has seen in recent times. The SARS-CoV-2 infection has the potential to cause multi-organ dysfunction. Though the virus predominantly affects the lungs, it can affect the heart in myriad ways. Heart failure (HF) is one such complication caused by the virus, both in patients with and without cardiovascular diseases. Different mechanisms have been proposed for the pathogenesis of HF in COVID-19 ranging from direct viral injury to indirect immune mediated damage. Patients can have different clinical presentations with either acute heart failure or chronic heart failure. Early recognition and prompt management is the need of the hour to prevent any mortality and morbidity.

Summary: COVID-19 can affect the heart in many ways. This article describes the mechanisms, clinical presentations and management of heart failure caused by COVID-19 infection.

Introduction
The ongoing Coronavirus disease-2019 (Covid-19) pandemic has affected around 200 countries worldwide. Till date, the total confirmed cases worldwide have crossed the 2 million mark with around 150,000 deaths. Covid-19 predominantly affects the respiratory system causing severe pneumonia/acute respiratory distress (ARDS). Varied effects on cardiovascular system are seen in form of acute coronary syndrome, myocarditis and heart failure. Majority of these patients have comorbidities with hypertension being the most common.1 Heart failure is a global health problem with significant mortality and morbidity. The ongoing pandemic has the potential to exacerbate this problem, thus causing significant burden on health resources which are already saturated due to high load of covid patients.

Pathogenesis
SARS-CoV-2 is a novel coronavirus which bears 80% similarity to the genetic structure of the SARS-CoV which caused the SARS outbreak in 2013.2 The SARS-CoV-2 virus contains multiple glycoprotein spikes (S protein) on their surface giving it a halo like appearance. The viral structure of the novel coronavirus has evolved from the SARS-CoV of 2013, thus having increased stability and increased affinity for receptor binding.3 Human angiotensin converting enzyme 2 (ACE 2) receptor has been identified as the target SARS-CoV-2.4 The host protease TMPRSS2 is responsible for priming the spike S protein which facilitates viral entry into cells.5 ACE 2 is present on a variety of tissues including heart, lung alveolar epithelial cells, kidney and gastrointestinal system. ACE 2 receptors are localized on the cell membrane and their turnover is increased in stress states/pro-inflammatory conditions like heart failure. Circulating ACE2 levels are increased due to cleavage of protein from membrane by ADAM17 protease.6 This increased turnover and expression of ACE2 on cardiac cells makes it susceptible to viral infection. SARS-CoV-2 can lead to myocardial injury via both direct and indirect mechanisms.

1. Direct mechanisms: SARS-CoV-2 can directly enter cardiomyocytes via ACE2 receptors. Under normal circumstances, ACE2 protein acts on angiotensin II and converts it to angiotensin 1-7. Angiotensin 1-7 has vasodilatory and anti-inflammatory action, thus balancing the pro-inflammatory effects of angiotensin II. During Covid-19 infection, the virus binds to ACE2 protein and enters the target cell. Simultaneously, it also causes downregulation of overall ACE2 activity of the cell.7 This downregulation of activity prevents ACE2 from acting on angiotensin II which causes unopposed activation of RAAS axis. This predisposes to a pro-inflammatory state associated with adverse cardiac remodeling, fibrosis and cardiomyocyte damage. Post viral entry, viral replication occurs inside cardiomyocytes and assembled virions are released, thus disabling or destroying the host cell in the process.

2. Indirect mechanisms
   i. Pro-inflammatory cytokine mediated damage: SARS-CoV-2 infection triggers a dysregulated immune response by causing depletion of lymphocytes with marked reduction in number of CD4+/CD8+ T lymphocytes.8,9 There is increased activation of mononuclear cells (macrophages) which produce pro-inflammatory cytokines like Interferon-beta, TNF and IL-6. These cytokines recruit more inflammatory cells and induce apoptosis of T-lymphocytes. Direct viral infection of T-lymphocyte has been demonstrated.10 Dysfunctional antibodies, not effective in neutralizing the virus, perpetuate the immune response. This dysregulated activation of macrophages produces abundance of pro-inflammatory cytokines –

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Inflammatory cytokines like TNF, IL-6, IL-18 cause damage to cardiac myocytes. They induce cardiac myocyte hypertrophy and re-expression of fetal gene program leading to adverse cardiac remodeling. Increased levels of proinflammatory cytokines can lead to transient and sustained contractile dysfunction via nitric oxide mediated mechanisms. Cardiomyocyte apoptosis is also induced by activation of extrinsic and intrinsic apoptotic pathways. Extracellular matrix remodeling via induction of cardiac fibroblasts and matrix metalloproteinases is also noted. In patients with heart failure, inflammatory cytokine levels are already elevated. Superimposed viral infection will exacerbate the overall cardiac damage and can worsen heart failure symptoms.

ii. Microvascular dysfunction: Increased cytokine production due to SARS-CoV-2 infection can lead to vascular endothelial damage causing microcirculatory dysfunction. ACE2 receptors localized on the pericytes of cardiac cells promote viral infection which can lead to endothelial dysfunction causing micro-infarcts. This exacerbates any pre-existing tissue damage and reduce overall cardiomyocyte function.

iii. Hypoxia mediated damage: SARS-CoV-2 primarily affects the respiratory system and the resultant hypoxemia causes tissue damage in various organs leading to multi-organ dysfunction. Hypoxia induces production of hypoxia inducible factor (HIF) which modulates the transcription of various genes. HIF regulates nitric oxide production and macrophage activation which can affect cardiac remodeling.

The pathogenesis of heart failure in Covid-19 has been summarized in Figure 1.

### Epidemiology and clinical presentation

There is scarce data at present regarding the incidence of heart failure in patients suffering from Covid-19. Majority of data available comes from the outcomes of patients hospitalized with Covid-19 related pneumonia. In a study cohort of 191 patients who were admitted with SARS-CoV-2 in China, heart failure was noted in 23% (n=44) patients during the hospitalization period. The incidence of heart failure was significantly higher in non-survivors as compared to survivors (52% vs 12%, p<0.0001). Patients who had cardiovascular disease at baseline were at higher risk of having complications and inhospital mortality. In a cohort of 274 cases which included both deceased and recovered patients, heart failure was noted in 34% with prior history of cardiovascular disease whereas 19% without any history of cardiac disease developed de-novo heart failure.

Patients with Covid-19 can present as:

i. Acute heart failure: Patients without underlying cardiac disease can present with acute decompensated heart failure resulting from myocarditis. De-novo presentation with cardiogenic shock has also been reported in patients infected with SARS-CoV-2. Heightened sympathetic stimulation as a result of the infection can precipitate stress cardiomyopathy.

ii. Exacerbation of chronic heart failure – Patients with underlying cardiovascular disease (CVD) are at high risk of contracting Covid-19. They may have exacerbation of pre-existing heart failure symptoms. Heart failure patients may also have ventricular arrhythmias either due to virus induced myocardial injury or underlying structural heart disease.

Significant majority of patients admitted with Covid-19 have baseline cardiovascular risk factors and have higher mortality rates. Covid-19 affected patients who have baseline cardiovascular disease and elevated troponins have highest mortality as compared to those without history of cardiovascular disease (69% vs 37%, p<0.05). Progressively increasing troponin and BNP levels is a bad prognostic marker as it portends to higher chance of mortality. Heart failure patients also have elevated levels of inflammatory markers (ESR, CRP, LDH) which have been shown to correlate with disease severity.

### Diagnosis

History and clinical examination point to the diagnosis. Echocardiographic features of reduced LV function (LVEF 40%) and global hypokinesia point to diagnosis of myocarditis whereas apical ballooning with basal hypercontractility point towards stress cardiomyopathy. Biomarkers like troponin and natriuretic peptides are frequently elevated and may indicate severity of disease. Cardiac magnetic resonance (CMR) imaging can be used to detect presence of myocardial edema (T2 hyperintense) as well as presence of necrosis and scar (Late gadolinium enhancement). CMR can also be helpful in differentiating viral myocarditis from stress cardiomyopathy.

### Management

Treatment strategies are tailored according to the clinical presentation of the patient.

i. Management of Covid related heart failure: Acute heart failure patients will require inotropes for stabilization of hemodynamic status. Diuretics will form the mainstay of therapy. Patients refractory to diuretics may also need vasodilator therapy. In patients with suspected myocarditis, pulse steroid
(intravenous methylprednisolone 1 gm × 3 days) therapy is needed to control disease activity. Patients having malignant arrhythmias associated with heart failure will need anti-arrhythmic drugs and DC cardioversion if necessary. Fluid balance needs to be maintained in a proper manner.

ii. Management in pre-existing CVD: Chronic heart failure patients need to be continued on guideline directed medical therapy (GDMT) including beta blockers, ACEI/ARB and mineralocorticoid receptor antagonists. Intravenous diuretics may be needed in patients with volume overload. Use of drugs which can precipitate HF like NSAIDs should be strictly avoided. Prevention is the best policy in these patients with baseline CVD as they remain at high risk of contracting the virus. Repeated hand washing and practicing social distancing will help to break the chain of the virus and keep this vulnerable group of society safe.

iii. Covid-19 specific therapy: A number of drugs are being tried for specific therapy. Hydroxychloroquine,21 lopinavir/ritonavir and remdesivir22 have been tried for their anti-viral properties with modest efficacy. In patients suspected to be having cytokine storm, IL-6 inhibitors (tocilizumab) have shown some benefit.23 Convalescent plasma therapy24 and IVIG are also being tested as potential therapeutic options. However, use of these drugs has potential to cause adverse cardiac events. Patients with heart failure are frequently on diuretics which can lead to electrolyte imbalance. These patients are prone to rhythm disturbances which can get compounded by use of drugs like hydroxychloroquine which are documented to cause QTc interval prolongation. Monitoring is required when these drugs are initiated in patients with cardiac disease.

iv. Use of ACEI/ARB in Covid-19 patients: A lot of debate has ensued regarding the safety of angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) in patients infected with SARS-Cov-2. Initial hypothesis suggested that ACEI/ARB use can increase ACE2 levels leading to increased susceptibility to viral infection. However, there is no definite evidence to support this hypothesis. Potential benefit of ACEI/ARB has been advocated as these drugs may prevent unopposed RAAS activation by angiotensin II which can prevent serious tissue damage in target organs.25 The ESC Hypertension Council has stated in a position statement that use of anti-hypertensive drugs including ACEI/ARB should be continued in patients and there is no evidence pointing towards harmful effect of ACEI/ARB.26

Conclusion

Covid-19 disease has the potential to cause multi-organ dysfunction. Patients with cardiac risk factors or baseline cardiovascular disease are more susceptible during these times. Patients can have de-novo heart failure or exacerbation of pre-existing heart failure. Prompt diagnosis and management is necessary to prevent morbidity and mortality.

Compliance with Ethical Standards

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