COVID-19 AND CARDIOVASCULAR SYSTEM

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An outbreak of pneumonia caused by Novel Coronavirus occurred in Wuhan, Hubei province of China in December 2019[1] and rapidly engulfed the whole world in just a couple of months. WHO had to declare it a Pandemic in Jan 2020. It is caused by a Novel coronavirus termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was later termed as COVID-19 by WHO. The virus shows very strong transmission capabilities (human to human and even human to animal) as compared to its predecessors SARS-CoV and MERS-CoV. COVID-19 human to human transmission is caused by droplet, contact and ocular entry. With an incubation period of 5 to 14 days most patients remain asymptomatic [2] which is the main reason of its fast undetected spread while most patients who become symptomatic develop only mild flu like illness but it can also rapidly progress to serious lung and cardiac injury in a small percentage of patients which ultimately leads to death.

There are two distinctive clinical stages to the disease; Replicative and Adaptive immunity stages. During replicative stage most patients have mild flu like illness, dry cough, fever and shortness of breath. Chest x-ray and computed tomography show pneumonia at this stage.[3] Certain patients also develop gastrointestinal symptoms (abdominal pain, diarrhea, nausea). Then comes the 2nd stage when adaptive immune response of the body kicks in and viral titers gradually decline leading to the symptom resolution. But a minority of patients develop critical illness and are at high risk of mortality. About 10% of the patients who become critically ill develop ARDS, acute cardiac injury and multi-organ failure mostly due to a marked inflammatory immune response of an individual's body called Cytokine storm.[4]

The SARS-CoV-2 gains entry into the host human cells through angiotensin converting enzyme 2 (ACE 2) which is expressed on lung, vascular endothelia, renal and cardiac tissue and small intestinal epithelium.[5,6] So, causing direct damage to the involved tissues via a viral cytopathic pathway and indirect damage due to exaggerated inflammatory immune response involving various markers i.e. CRP, IL-6, and IFN-γ to TNF-α.[1]

Although Respiratory involvement is the dominant clinical manifestation of COVID-19 but other organ system involvement is also being documented rapidly as time passes by and our understanding of the subject is evolving. This article is aimed at cardiovascular involvement in COVID-19 and its potential consequences on morbidity and mortality. Very less information is available on CVS involvement in COVID-19 but on the basis of the available data it is thought that some 8 to 12% of the patients develop cardiac involvement

When does CVS involvement start?

It has been observed that symptoms and signs of CVS involvement appear approximately a week after the upper respiratory symptoms.

What type of Cardiac injury/involvement?

There appears to be different manifestations of cardiac involvement which are as follows

1.Acute cardiac injury (defined as elevation of cardiac troponin I above 99th percentile upper reference limit) also called myopercarditis/myocarditis
2.Acute coronary event
3.Heart failure
4.Arrhythmias
5.Chronic cardiac injury/long term consequences
6.Impact of COVID-19 on Pre-existing CV disease

What are the pathological mechanisms behind the above manifestations?

Various pathological mechanisms are thought to be behind the involvement of cardiovascular system. But two most important mechanisms (7,8) are

1. Direct myocardial injury: As described previously SARS-CoV-2 gains entry into the host cells through ACE2 which acts as its receptor. ACE2 is highly expressed on cardiac and lung tissue and is very

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important in maintaining neurohumoral regulation of CVS system. So, when SARS-CoV-2 bind to ACE 2, it alters the signaling mechanism of ACE 2 and causes direct myocardial injury through cytopathic mechanism

2. Exaggerated inflammatory immune response/Cytokine storm: This type of response occurs in 2nd stage of the disease and represents critical and severe form of COVID-19. It is characterized by acute systemic inflammation and cytokine syndrome. Various markers of inflammation i.e. CRP, IL-6, and IFN-γ to TNF-α are found to be in high levels in circulation as evidenced by various studies till now.

Various other forms of pathological mechanisms are also thought to play an important role in CV injury which include

a. Electrolyte imbalances especially hypokalemia which precipitates arrhythmias

b. Plaque rupture and coronary artery thrombosis can also occur due to systemic inflammation and high shear stress caused by increased coronary blood flow.

c. Altered myocardial supply-demand ratio also plays an important role. This occurs due to increased cardiac metabolic demand caused by septicemia and decreased oxygen supply due to hypoxia caused by respiratory illness leading to myocardial injury

d. Iatrogenic factors are also thought to play a part in CV injury as various medications including corticosteroids and antivirals given during illness can cause myocardial injury

ACUTE MYOCARDIAL INJURY:

It is labeled when high sensitivity cardiac troponin I elevates above 99th percentile of the upper reference limit [9] and/or EKG abnormalities. It is a very feared and most commonly encountered CV abnormality and carries worse prognostic significance. Any of the above pathological mechanisms can cause this but direct myocardial injury and systemic inflammation leading to viral myocarditis remain to be the leading causes. Symptoms are usually palpitations, chest tightness and shortness of breath. Heart failure rapidly ensues in these patients causing pulmonary edema and cardiogenic shock. Among patients who died from COVID-19 reported by the National health commission of China (NHC), 11.8% of patients without underlying CV disease had substantial heart damage, with elevated levels of cTnI or cardiac arrest during hospitalization.[10]

ACUTE CORONARY EVENT:

The incidence of ST elevation myocardial infarction seems to be low in COVID-19 patients but there are some case reports. It is caused by plaque rupture and coronary thrombosis as described above.

HEART FAILURE:

Heart failure typically ensues in patients with myocarditis. According to a Chinese study heart failure had occurred in 52% of the patients who subsequently died and in 12% of the patients who were discharged from the hospital.[11]

ARRHYTHMIAS:

Any type of arrhythmia i.e. tachyarrhythmia or bradyarrhythmia can occur. A Chinese study of 138 patients with COVID-19 showed 16.7% incidence of arrhythmias. The incidence of arrhythmias was found to be higher (44.4%) in patients who required ICU admission but only 8.9% in those not requiring ICU care.[12]

CHRONIC CARDIAC INJURY OR LONG-TERM COMPLICATIONS:

As COVID-19 is a new disease to the world, it is too early to guess the long-term implications of the disease on CV system. But we can learn from previous SARS-CoV infection. A 12 year follow up survey on long term implications of SARS-CoV infection which was done on 25 recovered patients from SARS-CoV showed that 68% had hyperlipidemia, 60% had glucose metabolism disorders, and 44% had CV abnormalities.[13] So, a follow-up of recovered patients of COVID-19 would give us some more information about its long-term implications on CV system

ROLE OF EKG:

Several EKG changes have been documented including sinus tachycardia, ST elevation in specific region/segment, diffuse ST elevation with AVR depression, $S_1Q_3T_3$ pattern, AV block, multifocal ventricular tachycardia[14] and other non-specific ST-T changes.

ROLE OF CARDIAC BIOMARKERS:

Cardiac biomarkers as N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity

troponin I [9] are not only important in the detection of cardiac injury but also play an important part in determining the prognosis. [15]

ROLE OF IMAGING:

Transthoracic Echocardiography is paramount in detection of cardiac involvement. It may show global hypokinesia causing decreased LV ejection fraction, dilatation of LV, Pulmonary Hypertension and even Life-threatening cardiac tamponade complicating myo-pericarditis. Cardiac MRI (CMR) can also be done and its important findings include increased wall thickness, diffuse biventricular interstitial edema and hypokinesia, severe LV systolic dysfunction, LV dilatation, pericardial effusion and late biventricular gadolinium enhancement.[16]

COVID-19 AND PATIENTS WITH UNDERLYING CV DISEASES:

Majority of patients with COVID-19 recover in a few weeks but the patients with pre-existing CV abnormalities like hypertension, DM, coronary artery disease, CMPs and congenital heart diseases tend to have increased vulnerability to get the disease and these patients are more likely to suffer from the severe form of disease and worse outcomes. Many recent studies have demonstrated these facts. In one Chinese study of patients with severe symptoms of COVID-19, the percentages of the patients having hypertension, heart disease and arrhythmias were 58%, 25% and 44% respectively (12). Chinese Center for Disease Control and Prevention reported in a large case series (44,672 confirmed COVID-19 cases) that the patients with underlying CV disease had a case fatality rate of 10.5% and those with hypertension had 6%; both of which are higher than overall case fatality rate of 2.3%. [17] The basic mechanism behind these findings may be the fact that the patients with underlying CV diseases have reduced or impaired cardiovascular functional reserve. So, these patients should adapt proper preventive measures including frequent handwashing, social distancing, use of masks and cleaning and disinfecting commonly touched surfaces.

MANAGEMENT OF CV COMPLICATIONS:

Overall management of COVID-19 patients with CV complications or pre-existing CV disease remains the same as for the patients without COVID-19 but keeping in mind certain implications, precautions and following proper guidelines. Unnecessary use of cardiac biomarkers, echocardiography, coronary angiography, and CMR should be discouraged until and unless necessary and according to the guidelines. As recent American college of Cardiology guidelines recommend use of thrombolytics (if no contraindications exist) in patients with STEMI in suspected or confirmed case of COVID-19.(18) There are case reports of management of myopericarditis and heart failure with diuretics, inotropic support, hydroxychloroquine, antivirals (lopinavir/ritonavir), Interferon α-1b, Methylprednisolone, immunoglobulin, piperacillin-tazobactam, ventilatory support, continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO) with progressive clinical stabilization in some patients.[16,19]

A RISING CONCERN; USE OF RAAS INHIBITORS AND COVID-19

Recently there is a rising concern for use and safety of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) during COVID-19 pandemic. As discussed previously SARS-CoV-2 gains entry into host cells through ACE 2. ACEi and ARBs upregulate the expression of ACE 2 in various tissues including cardiac myocytes. So, there is increased concern of contracting COVID-19 in patients taking these medications but there is no study or clinical data to date which supports these concerns. So, it is being strongly urged that these medications shouldn't be discontinued abruptly as risks of discontinuation of these are already well known.[20]

SUMMARY:

Despite respiratory illness being the dominant clinical manifestation in COVID-19, recent data suggests that there may be significant interplay between CV disease (pre-existing or new onset during illness) and COVID-19. Our understanding of this relationship is still inadequate so further studies are required in this regard.

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