Cardiac Manifestations of Covid-19

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1.1 Introduction:

As the name indicates, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), popularly called covid-19, is primarily a respiratory illness but the growing clinical experience has shown that it can cause serious damage to heart and other organs of the body. World Health Organization (WHO) declared Covid-19, a pandemic more than a year ago on 11th March 2020 and despite the worldwide efforts to control it, the virus is still managing to ravage the human lives [(1)].

A significant amount of published medical literature is now available on Covid-19, reflecting gigantic ef-forts made by the scientific community across the globe. A quick PubMed search for the topic 'Covid-19 and Heart' returned a substantial list of 5460 articles, out of a total of 118,397 articles on 'Covid-19'. Unfor-tunately, however most case series involve a limited number of patients often less than 100. Moreover, there is no consistency on the findings reported in the available literature with regards to cardio-vascular involvement in Covid-19, possibly due to significant variation in patient selection, diagnostic criteria as well as severity of underlying Covid infection.

2.1 Pathophysiology of Covid-19:

SARS-CoV2 (or Covid-19) starts as an acute respiratory illness and droplet transmission is the primary mode of transmission. The virus uses its S-spike to bind to Angiotensin Converting Enzyme 2 (ACE-2) re-ceptors, which act as an entry point to the cell. These ACE-2 receptors are expressed in lungs as well as other tissues like Heart and Kidneys [(2)].

This relationship between viral entry and ACE2 receptors was the basis for the controversy surrounding the use of renin-angiotensin-aldosterone system antagonists (RAS blockers or ACE inhibitors), which in-crease ACE2 expression in animal studies and therefore can theoretically increase susceptibility to infec-tion. However, this inference was disputed in the position statements of all major cardiovascular societies in the UK, Europe and North America.

2.1.1 Acute disease progression in Covid-19 usually shows 3 distinct clinical phases, although with variable duration and some overlap [(3)]:

1. An early infection phase of viral response
2. A pulmonary phase – Abnormal chest imaging
3. A severe hyperinflammation phase (or Host's immune over-reaction)

A large majority (up to 81%) of patients with Covid-19 remain asymptomatic or develop only mild consti-tutional symptoms (like fever, cough, malaise). This 'early phase' is due to innate immunity mediated through monocytes and macrophages. Some patients progress to a 'Pulmonary phase' due to continuing inflammatory response and further pulmonary damage, hypoxemia, and cardiovascular stress. Only a mi-nority of patients develop a 'severe hyper-inflammation phase' as the host's inflammatory response con-tinues to amplify, despite a diminishing viral load [(3)]. This phase of hyper-inflammation can be seen as our own deranged hyper-active defence mechanism to fight the virus and is characterised by a profound cyto-kine storm leading to multiple organ failure and a possible fatal outcome [(4)].

Within the context of acute disease progression in Covid-19, lymphocytopenia is a prominent feature and a high proportion of critically ill patients show progressive lymphocytopenia. Patients with severe disease eventually develop high total white cells and neutrophil counts, while maintaining a low lymphocyte count [(5)]. Exaggerated systemic inflammation and cytokine storm may correlate with lymphocytopenia and is a hallmark of severe disease [(4)].

2.1.2 The mechanisms of cardiac injury by Covid-19 are not well established. Cardiac involvement or myocardial injury may happen by 3 possible mechanisms:

(i) Secondary to respiratory failure and hypoxemia
(ii) Secondary to wider systemic hyperinflammatory response
(iii) Direct Myocardial invasion by the virus

In most critically ill patients, a combination all three above are responsible to a variable extent. Milder forms of cardiac injury in the form of elevation of cardiac biomarkers is a prominent feature in Covid-19 and may still indicate worse prognosis as compared to those with normal biomarkers [(5)]. In autopsy stud-ies patients with myocarditis showed no evidence of direct viral infiltration suggesting systemic hyper-inflammation to be responsible [(6)].

3.1 Cardiac Involvement in Covid-19:

It is difficult to know the exact frequency of cardiac involvement in patients of Covid-19 because majority (up to 81%) remain asymptomatic or get mild illness, and therefore they simply self-isolate at home and do not undergo any medical examination or pathology tests. Data is largely available from hospitalised patients, who are likely to have been severely affected, and show that cardiac involvement is not uncom-mon. There has been a significant variation seen in the rates reported for cardiac involvement due to dif-ferences in the diagnostic criteria, types of investigations undertaken, severity of covid-19 infection and relatively small size of studies. Any pre-existing yet unknown cardio-vascular disease in these patients will add to difficulties in precise estimation of Covid-19 induced cardiac problems.

Cardiac involvement in Covid-19 patients may be in the form of:

1. Effect on heart rate, rhythm and blood pressure: Covid-19 patients are at an increased risk of arrhythmias and blood pressure abnormalities due to underlying co-morbidities, hypoxemia, metabolic derangements, systemic inflammation, or myocarditis. In one study of 138 hospitalised patients, palpitation was reported as a symptom in 7.3% of patients although significantly higher proportion of critically ill patients showed arrhythmias in the form of tachycardia, bradycardia or even asystole [(5)]. Specific arrhythmias like atrial flutter or fibrillation were reported in 7%, Ven-tricular tachycardia or fibrillation in 5.9% [(5,6)].

A high proportion of critically ill patients (25-31%)

showed hypertension [5,8]. It was difficult to know from retrospective data if this hypertension was due to the pre-existing illness, or a reaction to the critical illness, or a phenomenon related to potential derangements in ACE2 expression. As expected, some critically ill Covid-19 patients also showed significant hypotension requiring vas-opressor support [8].

2. Effect on Cardiac Biomarkers: Significant elevation in specific Cardiac biomarkers (like NT pro BNP, Troponin, CK, CK-MB) may represent cardiac stress or myocardial injury [6,9]. Studies that reported the frequency of elevated cardiac biomarkers, NT pro BNP was elevated in 28% (106/380), Troponin 17% (278/1659), CK18% (84/466) and CKMB 12% (133/1148) [5,6,7,8,9].

   Significant elevation in Troponin does not automatically mean a classical type 1 myocardial in-farction (MI) due to coronary occlusion but more likely reflect non-coronary causes or type-2 MI in a critically unwell Covid-19 patient [9]. Elevated cardiac biomarkers have shown significant prognostic value in hospitalised patients with Covid-19. In a study by Guo et al, Troponin T was found elevated in 27.8% of hospitalised patients. Those with elevated Troponin showed a mortali-ty of 59.6% vs 8.9% in those with normal level [6].

3. Myocarditis, Heart Failure and Cardiogenic Shock: Among the causes of death with Covid-19 in Wuhan cohort, myocarditis leading to myocardial damage and heart failure contributed to 40% of deaths, either exclusively or in conjunction with respiratory failure [6,7]. Moreover, those with confirmed diagnosis of heart failure showed a mortality rate of 64% [6,9]. The mortality risk asso-ciated with heart failure was more significant than age, diabetes mellitus, chronic pulmonary dis-ease, or prior history of cardiovascular disease [6]. In a case series 3 out of 4 critically ill patients with heart failure degenerated into cardiogenic shock.

   Mechanism of myocardial injury / myocarditis has been discussed in detail in section 2.1.2 above and likely to be related to cytokine storm and hyper-inflammatory state, rather than direct myo-cardial invasion by the virus. True prevalence of myocardial dysfunction in hospitalised patients with Covid-19 may never be fully apparent, given the difficulty in performing echocardiography in these patients requiring strict isolation.

   In a recent interesting Frankfurt Registry of 100 patients who had recovered from COVID-19, car-diac magnetic resonance (CMR) imaging performed at median 71 days from diagnosis of Covid-19; revealed cardiac involvement in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%), which was independent of pre-existing cardiac conditions, severity and overall course of the acute Covid-19 illness and recovery [10].

4. Acute Coronary Syndrome (ACS) and acute Myocardial infarction (AMI): can occur in pa-tients with COVID-19, but the incidence of such events is unclear.

   The mechanism of increased risk of ACS in Covid-19 patients may be due to heightened pro-thrombotic activity, as evidenced by significantly elevated D-dimer levels. Additionally, severe systemic inflammatory response (even in other illnesses like Influenza) is known to increase the risk of plaque rupture resulting in either a ST-elevation MI or non-ST-elevation MI due to endothe-lial and smooth muscle cell activation, macrophage activation, and tissue factor expression [11]. The inflammatory response can be so intense that even spontaneous coronary artery dissection (SACD) can occur [12].

   Although the above is possible, most cases of myocardial infarctions in critically ill patients with Covid-19 actually represent type-2 MI due to hemodynamic effects of hypoxia, sepsis and meta-bolic derangements rather than true coronary obstruction (type-1 MI).

   A rise and/or fall of Troponin is not sufficient to secure the diagnosis of acute MI, and this should be based on clinical judgement, symptom/signs, ECG changes, and imaging studies.

Conclusion:

Covid-19, despite being primarily a respiratory virus, has shown to cause serious damage to heart as well as other organs. Wide ranging abnormalities of heart rate, rhythm as well as blood pressure control are common. Elevation of specific cardiac biomarkers suggesting myocardial injury, myocarditis or cardiac stress is common. High proportion of critically ill patients develop heart failure and cardiogenic shock. Acute coronary syndromes have been reported but are not so common.

True estimates of the above forms of cardiac involvement by Covid-19 even in hospitalised patients may be difficult to obtain, due to problems in organising common investigations (like echocardiogram, cardiac MRI, Cardiac catheterisations etc) on a routine basis under strict isolation, to protect medical staff and di-agnostic facilities. One recent Cardiac MRI study on patients recovered from Covid-19 showed evidence of cardiac involvement in 78% of patients even after a median of 71 days after the initial diagnosis.

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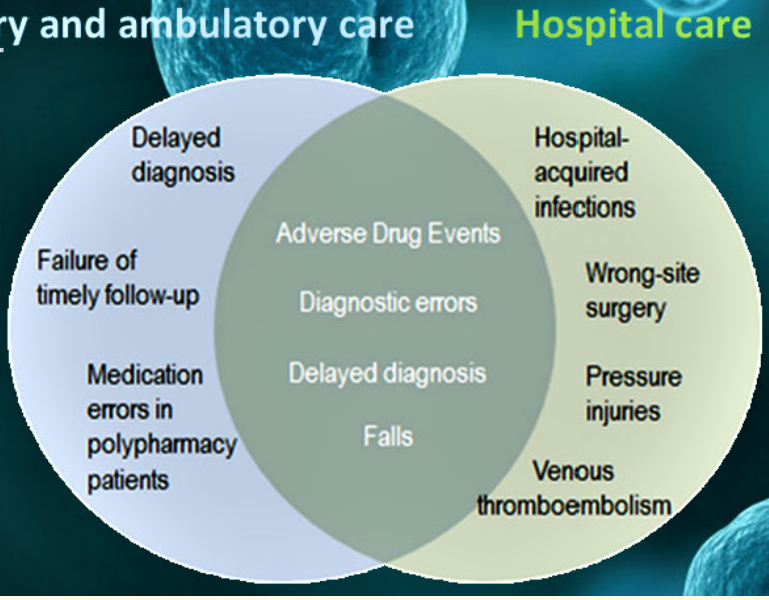

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