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COVID-19 Cardiac Manifestations and Presentation in Pre-Existing Cardiac Disease

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Abstract : The pandemic of COVID-19 is cause of high case fatality in patients with heart disease and hypertension. The thrombotic complication has been noted as a part of acute COVID-19 cardiovascular syndrome. Inflammed coronaries vulnerable to plaque rupture leading to thrombosis or spontaneous coronary artery dissection. The incidence of stress-related cardiomyopathy has been on rising trend during COVID-19 pandemic. In stress-induced cardiomyopathy, the role of acute stress-induced sympathetic over activity leading to catecholamine surge and subsequent myocardial dysfunction in the form of regional wall motion abnormality.

Key Words: Acute COVID-19 cardiovascular syndrome (ACovCs), Acute Cardiac Injury (ACI), Regional Wall Motion Abnormality (RWMA).

Introduction

The outbreak of pandemic of COVID-19 or coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, COVID-19) is cause of high case fatality rate of 10.5% in patients with heart disease and 6% in patients with hypertension. As the lung being the prime site of pathology in patients with COVID-19, the heart scores second as a target organ of SARS-CoV-2.

The postulated mechanisms for this high fatality rate is the possible abundance of ACE type 2 receptor in the cardiovascular system that strongly binds with the spike protein of COVID-19 and helps internalize into the cell resulting in Acute Cardiac Injury (ACI) (Zou, *et al.,* 2020; Wrapp, *et al.,* 2020). More than 7% of cases with COVID-19 are reported to have this type of Acute Cardiac Injury. In addition to the heart and lung, ACE-2 is expressed in the intestinal epithelium, vascular endothelium and the kidneys, providing a mechanism for the multi-organ dysfunction that can be seen with SARS-CoV-2 infection (Tikellis and Thomas, 2012; Zhang, *et al.,* 2020). ACE-2 receptor has a strong binding affinity to the surface spike protein of COVID-19 which after binding gets activated by type 2 transmembrane protease receptor and thus internalizes into the host cell (Wrapp, *et al.,* 2020; Clerkin, *et al.,* 2020; Rabi, *et al.,* 2020).

CLINICAL STAGES OF COVID-19

Stage I (early infection)

The early infection stage comprises viral response with mild constitutional symptoms: Fever >99.6°F, dry cough, diarrhoea, headache and signs such as lymphopenia, prolonged prothrombin time, increased D-dimer and raised lactate dehydrogenase.

STAGE II (PULMONARY PHASE)

It indicates host inflammatory response primarily affecting lungs with symptoms such as shortness of breath and air hunger, and signs such as PaO2/FIO2 ≤300 mm Hg, abnormal chest imaging, transaminitis and low normal procalcitonin.

STAGE III (Hyperinflammation)

It is a continuum of host inflammatory response of the pulmonary phase representing cytokine dysregulation/storm. The patient may show features of ARDS, shock/SIRS, ACI and heart failure. Lab findings elucidated in this stage are a rise in inflammatory markers, which include serum, lactate dehydrogenase, IL-6, D-dimer and ACI markers like troponin, NT-proBNP.

ACUTE COVID-19 CARDIOVASCULAR SYNDROME (Hendren 2020)

Inflammatory response in the form of systemic inflammatory response syndrome (SIRS)/cytokine storm inciting dysregulated immune response (Rabi, *et al.,* 2020) and inflamed plaque rupture leading to coronary artery thrombosis or spontaneous coronary artery dissection (Tersalvi, 2020) culminating in acute coronary syndrome (ACS).

a. Oxygen supply-demand mismatch due to hypoxia leads to ACS, especially type 2

myocardial infarction (MI). (Tersalvi, *et al.,* 2020)

b. Microvascular injury as a result of microvascular thrombi formation in continuum with disseminated intravascular coagulation or vasospasm or dysregulated immune response that surges in after viral response culminates into ACI and left ventricular (LV) dysfunction/heart failure. (Tersalvi, *et al.,* 2020)

c. Direct cardiotropic myocardial Injury (Tersalvi, *et al.,* 2020): SARS-CoV-2 induces cellular level damage by inducing oxidative stress and intracellular acidosis causing mitochondrial damage, hence promotes cardiac myocyte apoptosis.

d. SARS-CoV-2–induced ACE-mediated damage (Tersalvi, *et al.,* 2020): owing to abundant ACE-2 receptor in cardiovascular disorder, florid SARS-CoV-2 internalisation is promoted culminating into severe COVID-19. SARS-CoV-2 subsequently induces hyperstimulation of the ACE-1 pathway that incites vasoconstriction, inflammation, fibrosis and proliferation promoting adverse myocardial remodelling in addition to acute lung injury. On the other hand, SARS-CoV-2 inhibits the cardioprotective ACE-2 pathway comprising angiotensin 1–7 effect in the form of antifibrotic, antiproliferative, anti-apoptotic and vasodilatory property. Ultimately, SARS-CoV-2 brings up all the substrate required for heart failure.

MANIFESTATION OF COVID-19 ON THE CARDIOVASCULAR SYSTEM

- Acute myocarditis (including fulminant variant).
- ACS: MI type 1/2, non-ST-elevation MI (NSTEMI), unstable angina.
- Arrhythmias (supraventricular tachycardia/ventricular tachycardia/ventricular fibrillation (VF)).
- Heart failure with reduced and preserved ejection fraction (HFrEF/HFpEF), cardiogenic shock.
- Stress-induced cardiomyopathy.
- Acute pericarditis.
- Thromboembolic complications: arterial thromboembolism, deep vein thrombosis, intracardiac thrombus, microvascular thrombi, pulmonary embolism, stroke.

The thrombotic complication has been noted as a part of acute COVID-19 cardiovascular syndrome (ACovCs) in patients with severe COVID-19, which results due to substantial coagulation activation. This coagulation cascade is activated by SIRS. Endothelial dysfunction and procoagulant milieu are created by cytokine release/storm induced by virus invasion (Al-Ani, *et al.,* 2020). The procoagulant milieu is further exaggerated by hypoxia. Contrary to traditional belief, pulmonary vasculature thrombosis, both micro and macro in COVID-19, are mostly due to in situ pulmonary thrombosis rather than embolic phenomenon (Al-Ani, *et al.,* 2020). The warranted parenteral anticoagulant (heparin) therapy as prophylaxis and therapeutic option is justified.

MECHANISM OF MI IN COVID-19

ACI has been observed in 6-7% cases of patients with COVID-19. (Wang, *et al.,* 2020)

MI type 1 and type 2 have been proposed in patients with COVID-19 owing to

- Inflammed coronaries vulnerable to plaque rupture (Musher, *et al.,*2019) leading to thrombosis or spontaneous coronary artery dissection.
- Demand–supply mismatch in coronaries resulting from hypoxia, increased core body temperature, decreased cardiac contractility and increased heart rate, (Musher, *et al.,* 2019) respectively.

In COVID-19, the pattern of troponin release (rise or rise and fall) in the context of a clinical presentation of type 1 or 2 MI, myocarditis or cytokine/stress-related cardiomyopathy is not well defined(Hendren, *et al.,* 2020). A tenfold rise in mortality has been observed in patients with COVID-19 who experience a rise in high-sensitivity (hs)-troponin. All most half of the patients who died of COVID-19 had a rise in hs-troponin.

The incidence of stress-related cardiomyopathy has been on rising trend during COVID-19 pandemic than the prepandemic area due to psychological, social and economic stress associated with COVID-19 pandemic rather than COVID-19 disease itself (Jabri, *et al.,* 2020). Takotsubo syndrome is also known as stress-induced cardiomyopathy; though incompletely understood, putative mechanisms include epicardial spasm, microvascular dysfunction, direct adrenergic-receptor-mediated myocyte injury and systemic vascular effects that alter ventricular–arterial coupling. In stress-induced cardiomyopathy, the role of acute stress-induced sympathetic overactivity leading to catecholamine surge and subsequent myocardial dysfunction in the form of regional wall motion abnormality (Wittstein, 2016) (transient apical ballooning) not following any

coronary arterial territorial pattern is the rule.

ACI is characterised by marked cardiac troponin elevation accompanied by ST-segment elevation or depression on EKG, with normal epicardial coronaries (Wang, *et al.,* 2020). This stresses upon the fact that it is not the routine atherothrombosis rather inflammation ignited plaque rupture or coronary artery dissection that culminates into ACI as one of the putative mechanisms.

CARDIAC INJURY IN PATIENTS WITH PRE-EXISTING CARDIOVASCULAR DISEASE IN COVID-19

ACI in patients with COVID-19 was observed more in hypertensives and those with coronary heart diseases indicating the fact that pre-existing cardiovascular disorders are more prone to ACI. Approximately 30% and 60% of the patients with cardiac injury had a history of coronary heart disease and hypertension, respectively. This implies renin–angiotensin–aldosterone system (RAAS) activation in abundance has some important role to play with SARS-CoV-2 ACE-mediated damage leading to hyperstimulation of ACE-1 pathway that incites vasoconstriction, inflammation, fibrosis and proliferation promoting adverse myocardial remodelling in addition to acute lung injury.

Elderly patients with underlying diseases are more likely to be infected with SARS-CoV-2 and tend to be severely ill, especially those with hypertension, coronary heart disease and diabetes. The prevalence of comorbidities, that is, diabetes, cardio-cerebrovascular disease (CCVD) and hypertension among patients with COVID-19.

Arrhythmias in patients with covid-19

More than 15% of cases with COVID-19 experienced different types of arrhythmias. Arrhythmia is induced by hypokalemia in COVID-19 disease; this results due to the interaction between SARS-CoV2 and the RAAS system, which is a matter of concern indeed. Alone or complex interplay of dyselectrolytemia, electrically unstable inflamed myocardium, LV dysfunction, myocardial ischemia, hypoxia and acidosis due to acute lung injury may be the putative mechanism behind the origin of arrhythmias.

Cardiopulmonary arrest with pulseless electrical activity or VF has been reported during the recovery phase of their pulmonary illness in some anecdotal cases of COVID-19 with late myocardial dysfunction. Almost all forms of supraventricular and ventricular tachyarrhythmias have been documented. Bradyarrhythmias has been observed in COVID-19.

Drug-induced arrhythmias

QTc-prolonging drugs like chloroquine (CQ)/hydroxychloroquine (HCQ), azithromycin, lopinavir, ritonavir, which are used as trial therapeutics in COVID-19 alone or in combination, are to be used with caution owing to their Torsades de pointes generating potential.

Conclusion

The pandemic of COVID-19 is cause of high case fatality in patients with heart disease and hypertension. As the lung being the prime site of pathology in patients with COVID-19, the heart scores second as a target organ of SARS-CoV-2. The postulated mechanisms for this high fatality rate is the possible abundance of ACE type 2 receptor in the cardiovascular system that strongly binds with the spike protein of COVID-19 and helps internalise into the cell resulting in Acute Cardiac Injury. The thrombotic complication has been noted as a part of acute COVID-19 cardiovascular syndrome.

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