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Editorial

COVID-19 and sudden cardiac death: A new potential risk

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Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has taken the world by storm since its inception in Wuhan, China in December, 2019. As on 10th October, 2020 it has already affected more than 36 million people worldwide and has claimed approximately 10 lakhs lives according to the WHO (World Health Organization) estimates.[1]

SARS-CoV-2 unfavourably affects the elderly population and those with comorbidities.[2,3] COVID-19 is characterized by a high fatality rate.[3–5] Cardiovascular dysfunction adversely affects outcomes.[6,7] Sudden cardiac death (SCD) has emerge as one of the disturbing concern with COVID-19 infection.[8,9]

1. Lesson learn from the past

There is compelling evidence for an association between influenza epidemics and major adverse cardiovascular events like Myocardial infarction (MI), stroke, and SCD. These all may be prevented by influenza vaccination.[10,11] Influenza epidemics is also associated with higher risk of out-of-hospital cardiac arrest (OHCA).[12]

2. COVID-19 and SCD

Although the direct causal association of SCD and COVID-19 remain unproven, analysis of the present data suggests a plausible association. Increase incidence of SCD has been reported both in community and hospital settings.

Data from the Houston Fire Department shows a 45% jump during this COVID-19 pandemic, in the number of cardiac arrest calls that ended with patient dead.[13]

Data from Italy suggests a significant positive association with spread of COVID-19 and an increase number of OHCA. There is 58% rise in OHCA as compared to the previous year's.[14,15] A total of 103 patients out of 362 who had OHCA arrest were suspected or confirmed diagnosis of Covid-19 and were responsible for 77.4% of increase in cases of OHCA.[14] A two-fold rise in OHCA has also been noticed concurrent with COVID-19 pandemic in the registry data from Paris.[16] Although OHCA may be partly related to direct COVID-19 deaths, indirect effects like lockdown, behaviour changes, and health system issues may also be contributing.

Hospital data from China revealed that 27.8% of admitted COVID-19 patients had myocardial injury. Patients with elevated troponin levels had more frequent malignant arrhythmias (11.5% vs 5.2%). Overall mortality was much higher in elevated troponin levels (59.6% vs 8.9%)[17] A study of 146 hospitalized COVID-19 patients in China reported a cardiac injury incidence of 20% and a much higher mortality of 51.2% compared with 4.5% in patients with cardiac injury versus no cardiac injury.[18]

Study from Philadelphia reported 1.3% incidence of cardiac arrest amongst 700 patients admitted for COVID-19. Notably, all cardiac arrest occurred in patients admitted to intensive care unit (ICU) and the reported rhythm in 8 of the 9 patients was asystole or pulseless electrical activity with only 1 patient having Torsades des pointes (TdP).[19]

In a global survey carried out by Heart Rhythm Society Atrial fibrillation (21%) was the most commonly reported tachyarrhythmia, whereas severe bradycardia (8%) and complete heart block (8%) were the most common bradyarrhythmias. Respondent reported incidence of 4.8% for ventricular tachycardia/ventricular fibrillation arrest and 5.6% of pulseless electrical activity amongst hospitalized COVID-19 patients.[20] All of this evidence point out some association of increase mortality and SCD with COVID-19 infection.

3. Mechanisms of SCD in COVID-19

The mechanism of SCD in COVID-19 can be multifactorial (Table 1). However, due to lack of data, it remains difficult to ascertain the most common mechanism involved. Both tachyarrhythmia and bradyarrhythmia have been reported in COVID-19.[19] Life threatening arrhythmias have been variably reported from 10 to 16% of patients hospitalized for severe COVID-19, more commonly in the setting of elevated troponin indicating myocardial injury.[5,11,17,19] The arrhythmias and SCD often cluster in the ICU setting in patients with more severe systemic illness.[5] Multiple factors play an important role in such a setting, including hypoxia, acidosis, dyselectrolytemia, drug interactions, and importantly direct cardiac involvement in the form of myocarditis and acute coronary syndrome. Up to one third of patients admitted to ICU with COVID-19 have been shown to develop concurrent myocarditis or stress cardiomyopathy.[6,7,17,21] Arrhythmias in the acute setting of myocarditis may be due to a direct cytopathic effect, causing electrical imbalance, ischemia and gap junction dysfunction from impaired myocardial expression of connexins, or due to impairment of various ion channels. Because of this electrophysiological remodelling there is abnormal calcium handling and down-regulation of

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Table 1
Proposed causes of sudden cardiac death in COVID-19.

A	Acute Myocarditis including stress induce Cardiomyopathy
B	Post myocarditis sequel
C	Acute coronary syndrome
D	Hypoxia
E	High-grade systemic inflammatory state
F	Coagulation disorder
1	Pulmonary thromboembolism
2	Coronary thrombosis
3	Stroke
G	Cardiac tamponade
H	Electrolyte imbalance
I	Underlying genetic predisposition
J	Arrhythmiogenesis
1	Drug induce
2	Uncovering of underlying channelopathies
3	Direct arrhythmogenesis by COVID-19

potassium channels which leads to prolonged repolarization and abnormal conduction. This may lead to triggered activity or either circus-type re-entry or phase 2 re-entry.[22] In the post inflammatory stage, arrhythmia can be seen, due to variable degrees of myocardial scaring which promotes re-entrant.[23]

In an observational study of patients who have recently recovered from COVID-19 and underwent cardiac magnetic resonance (CMR) with a median duration of 71 days from infection, 78% were found to have some cardiac involvement and 60% had ongoing inflammation, followed by regional scar and pericardial enhancement. This is irrespective of preexisting conditions, the severity of illness and overall course of the COVID-19 presentation.[24] In a retrospective study of twenty-six patients recovered from COVID-19 and reported cardiac symptoms, 58% had abnormal CMR findings on conventional CMR sequences: myocardial edema was found in 54% and late gadolinium enhancement was found in 31%.[25] This persistent perimyocarditis and scaring after COVID-19 infection may be cause of SCD seen in some patients of COVID 19 much after recovery.

The menace of QTc interveal prolongation secondary to drug therapies in COVID-19 has received wide attention. Of all the QT prolonging drugs, antiarrhythmics have the highest risk of TdP with an incidence of 1–5%, while the risk from non-cardiovascular drugs is much lower at 0.001%.[26] HCQ/CQ have a known QT prolongation effect and TdP risk. However it is important to note that despite the possibility of drug-induced QT prolongation with HCQ/CQ, the risk of sudden cardiac death and TdP is very low, since the development of TdP is not linearly related to the baseline QTc interval. The Indian council of medical sciences retrospective case–control analysis of symptomatic healthcare workers receiving pre-exposure HCQ prophylaxis revealed no increased risk of adverse reactions or arrhythmias.[27] Despite using a higher dose of HCQ (800 mg od, followed by 600 mg in 6–8 h, then 600 mg od for 4 additional days), no arrhythmias or deaths were noted.[28] The Incidence of QTc prolongation in COVID patients treated with HCQ/CQ ranges from 7% to as high as 36% depending upon doses. However no ventricular arrhythmia, including torsades de pointes, were recorded.[29–32]

Other drugs including azithromycin and lopinavir/ritonavir have also been implicated to confer a higher risk of SCD, when used alone or in combination with other QTc prolonging drugs. Rosenberg et al reported a higher prevalence of abnormal ECG findings (27.1%) and cardiac arrest (15.5%) in patients receiving combination HCQ + Azithromycin (AZ) vs those on HCQ alone (27.3 and 13.7%), AZ alone (16.1% and 6.2%) or neither drug (14% and 6.8%).[33] The combination of azithromycin and hydroxychloroquine is a commonly implicated culprit with significantly more prolonged QTc interval by combination therapy as compared to either drug alone.[33,34] Guidelines have been formulated outlining importance of ECG screening with use of these drugs.[35,36]

A direct involvement of SARS-CoV-2 infection in QTc prolongation and subsequent TdP, is the matter remains under investigation. High-grade systemic inflammatory state of COVID-19 may be important proarrhythmic factor. Inflammation as a important risk factor for long QT-syndrome and TdP has been shown by many basic and clinical studies. Cytokines has direct electrophysiological effect on myocardium, IL-6, tumor necrosis factor (TNF) α, and IL-1 can prolong ventricular action potential duration. Inflammatory cytokines, via central hypothalamus-mediated (inflammatory reflex) and peripheral (left stellate ganglia activation) pathways, can induce cardiac sympathetic system hyperactivation which in patients with long QT can trigger life-threatening arrhythmic events.[37] QTc prolongation was commonly observed in subjects with elevated C-reactive protein from different inflammatory conditions, also robustly correlating with IL-6 concentrations.[38]

In the setting of a viral infection, pre-existing chronic cardiovascular diseases can become unstable due to increased metabolic demand, reduced cardiac reserve, acute inflammatory responses.[18] It has been shown that the inflammatory activity within coronary atherosclerotic plaques is exacerbated during systemic inflammatory response due to acute infection, making them prone to rupture and causes acute coronary syndrome.[39]

Fatal arrhythmias in COVID-19 may also result due to hypoxia because of, direct viral lungs involvement, cardiac dysfunction, or severe systemic inflammatory state, electrolyte derangements, intravascular volume imbalances, and drug side effects.[19] Hypoxia can lead to fatal arrhythmias by several ways. It increases cytosolic calcium levels leading to early and late depolarizations and temporal alterations in the action potential duration. It also increase the extracellular potassium levels, which decreases the threshold for depolarization, accelerating electrical conduction.[40] Hypoxemia can also cause reduced electrical coupling and tissue anisotropy due to dephosphorylation of connexin 43 in the gap junctions.[41]

Clinically significant heart blocks have also been reported in COVID-19.[19,42] Pulseless electrical activity and asystole secondary to hypoxia and acidosis have been associated with SCD in critically ill COVID-19 patients with ARDS receiving care in ICU setting.[19] Covid −19 infection is shown to cause endothelia dysfunction by endotheliitis, endothelial injury, endothelial cell dysfunction and impaired microcirculatory function in different vascular beds leading to various life-threatening complications of COVID-19.[43] COVID-19 predisposes to both arterial and venous thrombosis. The true prevalence of thrombosis associated with COVID-19 infection is unknown, as most studies to date do not include comprehensive investigation protocols. The pathophysiology of a hypercoagulable state is attributable to direct endothelial injury of the microvasculature. Moreover, the acute inflammatory state and the immobilization of patients in ICU further contribute to excess thrombosis. Acute thrombosis can manifest into SCD through acute pulmonary embolism and in situ pulmonary thrombosis or coronary thrombosis with subsequent myocardial infarction.[44] Up to 50% of the patients admitted in ICUs with COVID-19 pneumonia develop thrombotic events.[45,46] Pulmonary thromboembolism has been indeed most common thrombotic complication.[44–47] It is commonly reported from ICU setting, affecting up to one third of all critically ill patients.[45–48] Acute pulmonary embolism is a major concern that can act as a perpetuator of SCD. The high risk of thrombotic events has already prompted a widespread routine prophylaxis in the form of heparin in all hospitalized COVID-19 patients.

Acute coronary syndrome (ACS) because of coronary thrombosis (type I myocardial infarction) due to SARS-CoV-2 infection seems a real possibility, but has been limited to very few case reports.[49]

Type II myocardial infarctions secondary to persistent hypoxia and consequent demand-supply mismatch are more common and lead to myocardial injury. Antiplatelet therapies according to guidelines must be instituted once a diagnosis of ACS is made. Close monitoring is warranted as COVID-19 patients as they are also at high risk of bleeding due to consumption coagulopathy/disseminated intravascular coagulation, commonly seen in critically ill patients.[50]

Other mechanisms have been also been reported to predispose to SCD in COVID patients on a case to case basis. These include coronary artery dissection,[51] cardiac tamponad[52] and uncovering of underlying channelopathies[53] (which may be both due to direct infection and drug interactions).

4. Management

Prevention is the cornerstone of management of COVID-19. All hospitalized COVID-19 patients should have a baseline ECG to check QTc interval and look for other risk markers of tachy/brady-arrhythmias. Any high-risk feature should pre-empt further frequent ECG monitoring during the hospital stay. Drug treatment of COVID-19 has involved many unproven therapies or therapies with limited benefits. The physician should not forget the golden rule of medicine – "First do no harm", while choosing such a therapy. The whole prescription should be evaluated for drug interactions before prescribing a new medicine. Combination therapies which have clearly shown to cause significant QTc prolongation, such as hydrocycholoroquine-azithromycin, should be avoided as far as possible. A potentially pro-arrhythmic common variant, p.Ser1103Tyr-SCN5A, present in 1 out of 13 individuals of African descent has the potential to increase the risk of drug- and hypoxia-induced ventricular arrhythmias/sudden cardiac death and contribute to observed racial health disparities in the COVID-19 pandemic.[54] However role of genetic testing in this situation is not recommended at present. QTc-prolonging COVID-19-directed therapies, most notably the combination of hydroxychloroquine and azithromycin, should be limited to settings where careful cardiac monitoring can be done. Metabolic parameters including electrolytes, fluid volume and acidosis should be actively sought and treated at the earliest possible, especially in the ICU. Every patient deserves risk stratification for venous thromboembolism and acute coronary syndrome based on his/her clinical background and available information. Patients with moderate to severe COVID-19 deserve thromboprophylaxis in the form of heparin to prevent occurrence of fatal thromboembolic events. Anti-platelets should be used where suitable. However, watchful monitoring for bleeding manifestations should be continued.

Dealing with a SCD situation with immediate cardio-pulmonary resuscitation (CPR) may prove to be difficult while ensuring healthcare worker safety. Thus, pre-emptive preparedness for starting immediate chest compressions and early endotracheal intubation should be planned beforehand in all ICUs. Donning of level 3 personnel protective equipment by healthcare workers, transferring deteriorating patients to negative pressure suits, use of mechanical compression devices, using bag-mask devices with filters and tight seals, using clear plastic sheets/boxes while intubation under video laryngoscopy, using HEPA filters in ventilatory equipment and minimizing closed circuit disconnections, are some of the precautions that have been recommended to prevent transmission during CPR.[55] CPR in COVID-19 patients without proper PPE is a matter of controversy. Most do not recommend to do CPR in this situation.

The exact arrhythmic risk related to COVID-19 patients with less severe illness or those who recover from the acute phase of the severe illness is currently unknown. Improved understanding of this is critical, primarily in guiding decisions on whether additional arrhythmia monitoring is needed after discharge or whether an implantable cardioverter defibrillator or wearable cardioverter defibrillator will be needed in those with impaired left ventricular function.

To conclude, an increasing trend of SCD concurrent with SARS-CoV-2 pandemic has been observed. SCD is often multifactorial with interlinked mechanisms. Keeping a high index of suspicion with active risk stratification followed by suitable preventive measures hold the key towards reducing SCD incidence.

Declaration of competing interest

None declared.

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