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Review Article

Cardiology in the COVID-19 Era - The Changing Paradigms -

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SUMMARY

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has attained the distinction of a global pandemic, affecting more than 185 countries. The impact of COVID-19 in the practice of cardiology extends beyond the clinical Cardiovascular (CV) manifestations of the disease. Many treatment modalities used in the treatment of COVID-19 have direct or indirect effects on the CV system. Management of CV disease in patients with proven or suspected COVID-19 infection warrants modification of existing practices and guidelines so as to suit the changed health care environment. The safety of health care personnel becomes an important consideration in the setting of this highly contagious pandemic. Furthermore, long-term cardiovascular consequences of COVID-19 need to be determined for appropriate follow-up of patients recovering from the infection. We review the data available till date on the various aspects of the impact of COVID-19 on the heart and the practice of cardiology.

Keywords: COVID-19; Heart; Cardiology; SARS-CoV-2; Myocarditis

INTRODUCTION

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first reported in December 2019 from Wuhan, China, has attained the distinction of a global pandemic since March 2020, affecting more than 185 countries [1,2]. In the absence of curative treatment or preventive vaccines, the egregious impact of COVID-19 on public health and health care delivery systems across the globe has been unprecedented. The impact of COVID-19 in the practice of cardiology extends beyond the clinical Cardiovascular (CV) manifestations of the disease, and involves multiple aspects ranging from the deleterious effects of the infection on patients with pre-existing cardiovascular disease, to the delayed seeking of medical attention for CV emergencies owing to the apprehension about the pandemic. This is a review of the data available till date on the various aspects of the impact of COVID-19 on the heart and the practice of cardiology.

EPIDEMIOLOGY

Patients with CV risk factors such as advanced age, male sex, diabetes mellitus, systemic hypertension and obesity, as well as patients with established CV disease have been identified as particularly vulnerable populations with increased morbidity and mortality from COVID-19 [3,4]. In a retrospective cohort study of 72,314 cases from China, the age-unadjusted mortality in patients with CV co-morbidities was five-fold higher (10.5%) than the rest of the cohort [5].

Analysis of data from different parts of the world has revealed that increasing age is an important risk factor for severe course of COVID-19 infection [2]. In a meta-analysis of 6 studies (n = 1527), hypertension and cardio/cerebrovascular diseases were present in 17.1% and 16.4% of hospitalized COVID-19 patients respectively, and conferred ~2-fold and ~3-fold higher risk respectively, for more severe COVID-19 [6]. From the available data, it can be inferred that although patients with pre-existing CVD may not be more susceptible to contracting SARS-CoV-2, they are prone to develop more severe complications of COVID-19 with increased mortality [7].

The higher mortality in patients with CV comorbidities may be either directly attributable to the underlying CVD or a mere coincidence. CVD, a marker of accelerated ageing and immune system dysregulation, may indirectly affect the prognosis in COVID-19. Advancing age, a risk factor for CVD as well as an important determinant of COVID-19 fatality, may be the connecting link between the two.

PATHOPHYSIOLOGY

SARS-CoV-2 is a novel beta coronavirus. Corona viruses are enveloped, positive-sense single-stranded RNA viruses with surface projections that correspond to surface spike proteins [8]. Binding of the SARS-CoV-2 spike protein to ACE2 protein on the host cell facilitates entry of the virus into the cell via receptor-mediated endocytosis involving cell surface associated transmembrane protein serine 2 (TMPRSS2) [9].

ACE2 is a membrane protein that is highly expressed in the lungs, heart, blood vessels, kidneys and gastrointestinal tract [10]. The tight interaction of SARS-CoV-2 with the human ACE2 receptor binding domain facilitates its greater transmissibility among humans [11]. Within the host cell cytoplasm, the released viral genome RNA replicates leading to newly formed genomic RNA, which is processed into virion-containing vesicles that fuse with the cell membrane to release the virus. The high expression of ACE2 in type 2 lung alveolar cells explains the predominant respiratory symptoms in COVID-19 [12]. The disruption of RAS/ACE2 by SARS-CoV-2 infection plays a pathogenic role in severe lung injury and respiratory failure in COVID-19 [2].

The mechanisms of CV injury from COVID-19 are multifactorial. More than 7.5% of myocardial cells have positive ACE2 expression, which could mediate SARS-CoV-2 entry into cardiomyocytes, resulting in direct cardiotoxicity [13]. After cell entry via ACE2, SARS-CoV-2 appears to downregulate ACE2 expression, which is vital to maintenance of cardiac function [14].

SARS-CoV-2 can induce cytokine release syndrome or 'cytokine storm' by intense release of proinflammatory cytokines such as interleukin (IL)-1, IL-6, T helper 1 cytokine interferon-gamma, and tumour necrosis factor-alpha (TNF-α) [15,16]. The immune-mediated hyperinflammation and altered immuno metabolism may lead to vascular inflammation, plaque instability, myocardial inflammation, hypercoagulable state, and direct myocardial suppression [17,18]. Cluster of Differentiation 209 (CD209), another receptor through which SARS-CoV-2 may enter cells, is expressed in macrophages promoting invasion of virus into immune cells in cardiac and vascular tissues [19]. Cardiac injury can lead to activation of the innate immune response, as well as the adaptive auto-immune mechanisms through molecular mimicry, thereby aggravating the damage [19]. The infection of endothelial cells or pericytes could lead to severe microvascular and macrovascular dysfunction as well.

The histopathological findings in cardiac tissue vary from minimal change to interstitial inflammatory infiltration, fibrosis,

myocyte hypertrophy and myocyte necrosis [20]. Microthrombosis and vascular inflammation are demonstrated in the vasculature.

CARDIOVASCULAR MANIFESTATIONS OF COVID-19

The spectrum of CV abnormalities observed in COVID-19 may vary from subclinical myocardial injury as evidenced by elevation of cardiac biomarkers, to myocardial infarction, myocarditis, cardiac arrhythmia, arterial and Venous Thromboembolism (VTE), cardiogenic shock and cardiac arrest. Cardiac injury was a common finding (19.7%) in a Chinese cohort of 416 patients, of whom 57 died. In the patients who died, 10.6% had Coronary Artery Disease (CAD), 4.1% had HF, and 5.3% had cerebrovascular disease. In multivariable adjusted models, cardiac injury was significantly and independently associated with mortality (Hazard Ratio [HR]: 4.26) [7].

MYOCARDIAL INJURY

Myocardial injury, generally defined as the elevation of high-sensitivity cardiac troponin (hs-cTn) above the 99th percentile of its upper limit of normal or evidence of new electrocardiographic or echocardiographic abnormalities, occurs in 8% of patients with COVID-19 infection and correlates with disease severity [15,21].

Myocardial injury may result from ischaemia, as well as non-ischaemic aetiologies (Table 1).

Table 1: Cardiovascular manifestations in COVID-19.

1. Myocardial injury
• **Ischaemic:**
- **Type 1 MI**
• Plaque rupture
• MINOCA
•Disseminated intravascular coagulation
- **Type 2 MI**
• Hypoxaemia
• Vasoconstriction
• Tachycardia
• **Non-ischaemic**
- Acute or fulminant viral myocarditis
- Stress cardiomyopathy
- Cytokine storm
2. Arrhythmia
• Tachyarrhythmia
• Bradycardia
3. Venous thromboembolism
• Deep vein thrombosis
• Acute pulmonary embolism

Ischaemic

Type 1 MI: Systemic Inflammatory Response Syndrome (SIRS) evoked by viral infections has been shown to increase the risk of plaque rupture and thrombus formation in the epicardial coronary arteries, resulting in type 1 MI with or without ST elevation [22]. Local microvascular inflammation during SARS-CoV-2 infection of the pericytes and resultant severe microvascular dysfunction can result in Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) [23]. DIC, a life-threatening complication with an incidence of 71% in non-survivors with COVID-19, has been implicated in the thrombosis of epicardial coronary arteries and coronary microvasculature, resulting in focal myocardial necrosis, and severe myocardial dysfunction [24].

Type 2 MI: Severe respiratory infection can lead to type 2 MI resulting from a mismatch between myocardial oxygen supply (which is decreased due to hypoxaemia and vasoconstriction) and myocardial oxygen demand (increased owing to the haemodynamic effects of infection and respiratory distress) in patients with pre-existing coronary artery disease [2].

Non-ischaemic

Acute/fulminant myocarditis: Myocarditis appears in COVID-19 patients several days after the onset of fever. The reported incidence of acute heart failure was 33% in critically ill patients with COVID-19 without a past history of LV systolic dysfunction [25]. It needs to be noted that myocardial dysfunction can develop in COVID-19 with mild or absent respiratory symptoms [26]. Limited clinical experience indicates that SARS-CoV 2 may lead to fulminant myocarditis [27]. Myocarditis should be suspected in the presence of acute-onset chest pain, heart failure or cardiogenic shock; repolarization abnormalities in the ECG; cardiac arrhythmia; and/or haemodynamic instability. Echocardiography may reveal LV dilatation and global/multi-segmental LV hypocontractility. There will be significant increase in cardiac troponin and BNP/NT-proBNP levels, in the absence of significant CAD [2].

Stress-induced cardiomyopathy: Mid-Left Ventricular (LV) hypokinesia and basal-to-mid LV hypokinesia, patterns consistent with mid-ventricular stress cardiomyopathy and reverse Takotsubo stress cardiomyopathy respectively, have been reported in COVID-19 [28,29].

Cytokine storm: It is postulated that proinflammatory cytokines depress myocardial function immediately through activation of the neural sphingomyelinase pathway and subacutely (hours to days) via nitric oxide-mediated blunting of beta-adrenergic signaling [30].

ARRHYTHMIA

In COVID-19, cardiac arrhythmia may be the initial presenting feature, which could either be the manifestation of underlying myocardial injury or the effect of medications used in the management of the disease. A study of 137 patients in Wuhan showed that 7.3% had experienced palpitations as one of their presenting symptoms for COVID-19 [31]. The incidence of arrhythmias was found to be more common (44.4%) in patients in the Intensive Care Unit (ICU), as compared to the non-ICU patients (6.9%) [32]. The interaction of SARS-CoV2 with RAAS may also increase the propensity to develop cardiac tachyarrhythmias secondary to hypokalemia [33].

Transient sinus bradycardia has been reported as a possible manifestation of COVID-19. Severe hypoxia, inflammatory damage of cardiac pacemaker cells, and exaggerated response to medications are proposed to be the possible triggers. Bradycardia, secondary to the direct action of high levels of pro-inflammatory cytokines on the Sinoatrial (SA) node, may be a harbinger of cytokine storm [34].

VENOUS THROMBOEMBOLISM (VTE)

Prolonged immobilisation, hypercoagulable state, active inflammation, hypoxaemia and DIC increases the propensity of patients with COVID-19 to develop VTE. The prevalence of ultrasound-confirmed deep venous thrombosis in patients with COVID-19 is 22.7% [35]. Sudden unexpected worsening of

respiratory distress, new/unexplained tachycardia, unexplained fall in BP, (new-onset) ECG changes suggestive of Pulmonary Embolism (PE), and signs of deep vein thrombosis of the extremities should trigger a suspicion of PE [2].

DIFFERENTIAL DIAGNOSIS

In COVID-19-infected patients with clinical presentation compatible with CVD, the three main aetiologic possibilities which should be considered include:

1) Cardiac events unrelated to or exacerbated by the infection, such as ACS, acute HF, arrythmias

2) Cardiac injury as a direct consequence of the infection

3) Clinical syndromes mimicking CV events, in the absence of cardiac injury, such as septic shock [36].

CARDIAC BIOMARKERS

Cardiac Troponin (cTn)

As discussed earlier, elevation in serum Troponin indicates myocardial injury, which may be multifactorial in origin. High sensitivity cardiac troponin (hs-cTn) levels have been found to correlate with disease severity and mortality rate in COVID-19, even after adjustment for other comorbidities [37].

A retrospective single-centre case series of 187 patients with COVID-19 found that patients with underlying CVD were more likely to have cardiac injury (troponin elevation) compared with patients without CVD (54.5% *vs* 13.2%). In-hospital mortality was 7.6% for patients without underlying CVD and normal troponin, 13.3% for those with CVD and normal troponin, 37.5% for those without CVD but elevated troponin, and 69.4% for those with CVD and elevated troponin [4].

In addition to the serum concentration of cTn, the pattern of rise was also found to be a significant prognostic marker in patients with COVID-19. A persistently rising trend of cTn was observed among non-survivors (from symptom onset till death) while the levels remained unchanged among those who survived [21]. Thus, monitoring of cTn levels may serve as a tool for prognostication of hospitalized patients.

Elevated troponin levels have also been reported to be associated with a higher incidence of haemodynamically unstable Ventricular Tachycardia (VT)/Ventricular Fibrillation (VF) (11.5% *vs* 5.2%, $p < 0.001$) [4].

BNP/NT-proBNP

BNP/NT-proBNP are frequently elevated among patients with severe inflammatory and/or respiratory illnesses, indicative of haemodynamic myocardial stress and HF[38,39].The concentrations of BNP/NT-proBNP in a patient with COVID-19 should be seen as the combination of the presence/extent of pre-existing cardiac disease and/or the acute haemodynamic stress related to COVID-19. To a certain extent, the release of BNP/NT-proBNP is associated with the extent of right ventricular haemodynamic stress [36].

EVALUATION OF THE HEART

ELECTROCARDIOGRAM (ECG)

The ECG diagnostic criteria for various conditions remain the same in patients affected by SARS-CoV-2 infection. A myriad of electrocardiographic findings, ranging from sinus tachycardia and bradycardia, to conduction disturbances and ventricular tachyarrhythmias, are expected in patients with COVID-19 [40].

CARDIAC IMAGING

The appropriate use criteria for cardiovascular imaging needs revision in the wake of the peculiar COVID-19 scenario. Imaging modalities which entail a greater risk of aerosol generation and/or exposure to greater number of HCP should be sparingly used.

ECHOCARDIOGRAM

Echocardiogram - Transthoracic (TTE), Transesophageal (TEE) and stress-should be avoided in patients in whom test results are unlikely to change the management strategy. In COVID-19 positive patients, patient contact with the machine and the sonographer should be minimized by focusing solely on the acquisition of relevant images necessary to answer the clinical question. Point of Care Focused Ultrasound (POCUS), Focused Cardiac Ultrasound Study (FoCUS) and bedside echocardiography are effective options to screen for CV complications of COVID-19 infection [36].

Since TEE is associated with greater exposure of HCP to aerosols with large viral load, all patients undergoing TEE should be tested for SARS-CoV-2 status. Planned procedure may be undertaken using standard protective tools in case of two negative results within 48 hours with no suspicious symptoms. If TEE is deemed absolutely necessary in patients with positive SARS-CoV-2 test or unknown status, level II protection is warranted [36].

In an echocardiographic study done on 100 patients with COVID-19, the most common abnormal finding was RV dilatation and dysfunction (39%), followed by LV diastolic dysfunction (16%) and LV systolic dysfunction (10%). It was found that RV dysfunction correlated with elevated cTn and poorer clinical status. In patients presenting with clinical deterioration at follow-up, acute RV dysfunction, with or without deep vein thrombosis, was commoner than acute LV systolic dysfunction (20%) [41].

CARDIAC COMPUTED TOMOGRAPHY (CT)

Cardiac CT Angiography (CCTA) may be the preferred non-invasive imaging modality to diagnose CAD since it reduces the time of exposure of patients and personnel [42,43]. Cardiac CT may be preferred to TEE in order to rule-out Left Atrial Appendage (LAA) and intracardiac thrombus prior to cardioversion [42]. Concomitant chest CT may also reveal features diagnostic of COVID-19.

NUCLEAR IMAGING

Nuclear cardiology tests should be utilized sparingly, as they require long acquisition times [44]. Positron Emission Tomography (PET) minimizes the acquisition times. Some specific indications would be the use of 1) PET-CT in patients with suspected endocarditis of prosthetic valves or intracardiac devices (when other imaging modalities are inconclusive, to avoid TEE), and 2) Single Photon Emission Computed Tomography (SPECT) or PET for evaluation of suspected CAD (when CCTA is not appropriate or available). The shortest duration of scan time and exposure, standard dose imaging with rapid protocols of data acquisition, and attenuation corrected imaging are recommended wherever appropriate [36].

CARDIAC MAGNETIC RESONANCE (CMR) IMAGING

The risks of contamination during a CMR scan is probably similar to a CT scan, but lower than during an echocardiographic study. Shortened CMR protocols focused on the clinical problem

are recommended [45]. CMR is the preferred imaging modality in acute myocarditis [46]. Renal function should be ascertained before contrast use.

EXERCISE TESTING

Since tachypnoea associated with exercise has the potential to increase the production and dispersion of aerosols, performance of exercise testing - ECG, echo or nuclear- is discouraged in COVID-19 suspect or positive patients and, in general, in every patient during the COVID-19 epidemic [36]. Alternative diagnostic methods for CAD such as CCTA should be used whenever possible.

CARDIAC CONSIDERATIONS IN COVID-19 TREATMENT

As COVID-19 is a novel disease, most treatment modalities used in its treatment at present are investigational, many of which have direct or indirect relevance to the CV system. Moreover, the established treatment protocols in the management of cardiac disease and the cardiac drug regimens need to be modified, while managing patients with proven or suspected COVID-19 infection. This section focuses on those aspects of treatment which are relevant to the heart.

Hydroxychloroquine/Chloroquine

Chloroquine is an antimalarial drug with in vitro antiviral activity against SARS-CoV-2 [47]. In addition to the antiviral effect of chloroquine, hydroxychloroquine has a modulating effect on activated immune cells to decrease IL-6 expression [48]. Non-randomised observational studies have suggested the efficacy of hydroxychloroquine in promoting conversion to viral negative status and shortening the disease course [49]. Results of ongoing clinical trials of chloroquine/hydroxychloroquine efficacy in the treatment of SARS-CoV-2 are awaited.

Although rare, chloroquine and hydroxychloroquine are reported to cause Atrioventricular (AV) blocks and prolonged QTc, with the risk of Torsade De Pointes (Tdp)/Sudden Cardiac Death (SCD) [50]. A recent metanalysis on arrhythmogenic cardiotoxicity of quinolines and structurally related antimalarial drugs suggested that this risk is minimal (no events of SCD, documented VF or TdP in 35,448 individuals, 1207 of whom were taking chloroquine) [51]. However, during COVID-19 infection, the QT-related risk may be amplified by concomitant use of other QTc-prolonging drugs and/or electrolyte imbalances (hypokalaemia, hypomagnesaemia and/or hypocalcaemia) [50]. Conduction disturbances and hydroxychloroquine-associated myocarditis are rare and appear to be linked mostly to long-term treatment.

Azithromycin

Azithromycin, a macrolide antibiotic with in vitro antiviral activity, has been proposed as an effective adjunct to hydroxychloroquine in COVID-19 through unclear mechanisms [52]. Azithromycin has been reported to be associated with QTc prolongation and TdP mainly in individuals with additional risk factors [53,54]. The CYP3A4 inhibitory effect of azithromycin, although weak, has the potential to interfere with hydroxychloroquine metabolism, thereby enhancing the risk of QT prolongation induced by combination therapy. However, the association of chloroquine and azithromycin has shown an acceptable safety profile in studies evaluating the combination for the prevention and treatment of malaria in Africa [55,56].

Antiviral therapy

Lopinavir/ritonavir, the protease inhibitors used in the treatment of COVID-19, have been reported to prolong PR and QT intervals, resulting in high-grade AV blocks and rarely torsade de Pointes [50]. Being potent inhibitors of CYP3A4, this combination has the potential to decrease the metabolism and potentiate the effect of various drugs including hydroxychloroquine, ticagrelor, statins, and factor Xa inhibitors such as apixaban and rivaroxaban, while decreasing the serum concentration of active metabolites of clopidogrel and prasugrel [57].

Ribavirin, although not known to cause cardiac abnormalities directly, can increase the levels of lopinavir/ritonavir. It has also been reported to reduce the effect of warfarin [58].

Remdesivir, the investigational drug being used in COVID-19, has limited information available about its adverse effects, apart from an isolated report of hypotension and bradycardia in a patient with Ebola [59].

Immunomodulatory Therapy

Corticosteroids, apart from causing fluid retention, electrolyte derangement, and hypertension, generally have a relatively safe cardiovascular profile. However, high dose intravenous methylprednisolone has been reported to cause acute symptomatic sinus bradycardia and rarely, Atrial Fibrillation (AF) and VT [60,61].

Interferon (IFN) alpha 2b has been shown to be beneficial in the treatment of COVID-19. Interferon can cause direct cardiac myocyte toxicity and disorders of the cardiac conduction tissue [62]. The most common reported adverse cardiac side effects of interferon therapy in patients with hepatitis have been dilated cardiomyopathy, atrial extrasystole, myocardial ischaemia and reversible hypertension [63].

IL-6 inhibitors such as Tocilizumab and Sarilumab,which are being tried in COVID-19, are not known to have any significant cardiac side effects [50].

THE CONUNDRUM OF ACE INHIBITORS (ACEI) AND ANGIOTENSIN RECEPTOR BLOCKERS (ARB)

Some experimental findings had suggested that RAAS inhibitors cause a compensatory increase in tissue levels of ACE2, raising unsubstantiated concerns that ACE-inhibitors or ARBs may be detrimental in patients exposed to SARS-CoV-2 [12,64,65]. However, the available data from blood samples suggest that there is no association between circulating levels of ACE2 and use of RAAS antagonists [66]. Moreover, a potentially protective influence of ARBs has been suggested from some experimental models [67].

A recent observational study of over 8910 patients from 169 hospitals in Asia, Europe, and North America, did not show a harmful association of ACEIs or ARBs with in-hospital mortality [68] while a Wuhan study demonstrated that in 1128 hospitalized patients, the use of ACEI/ARB was associated with lower risk of COVID-19 infection and its serious complications [69]. Hence all major CV societies have recommended continuation of ACEIs or ARBs in patients taking these drugs.

MECHANICAL CARDIOPULMONARY SUPPORT (MCS)

Mechanical cardiopulmonary support in respiratory failure has been reported with variable success. In the setting of cardiogenic shock related to COVID-19, intra-aortic balloon pump (IABP), or

veno-arterial ECMO should be considered. The improved survival of patients with fulminant myocarditis was reported with the use of Mechanical Circulatory Support (IABP and/or MCS) during the 2009 H1N1 pandemic in Japan [70]. Successful treatment of COVID-19-associated acute myopericarditis (presenting with cardiogenic shock and no respiratory symptoms) with IABP support has been reported [28]. An ideal strategy in cardiogenic shock would be to convert veno-venous ECMO (adequate for ARDS) to veno-arterial-venous ECMO.

MANAGEMENT OF CARDIAC EMERGENCIES IN THE COVID ERA

Although the objectives and goals of treatment of cardiac diseases remain the same, various concerns such as safety of Health Care Personnel (HCP) and availability of infrastructure come to the fore, while choosing the modality and timing of treatment in the setting of a contagious pandemic. This mandates the modification of existing practices and guidelines so as to suit the changed health care environment. Various cardiovascular societies have come out with guidelines in this regard.

ACUTE CORONARY SYNDROME

Non ST Elevation Acute Coronary Syndrome [NSTE-ACS]

The treatment strategy for patients with NSTE-ACS is guided by risk stratification as per existing guidelines [71]. However, testing for SARS-CoV-2 should be performed as soon as possible following first medical contact. Patients waiting for the SARS-CoV-2 test results must ideally be managed in a dedicated area in the emergency department, whenever feasible. Patients, who test positive, should be transferred to a COVID-19 hospital equipped to manage COVID-19-positive patients [36].

Patients with Troponin rise and no acute signs of instability such as ECG changes or recurrence of pain may be managed with a primarily conservative approach. Non-invasive imaging using Cardiac CT angiography (CCTA) may be utilized to hasten risk stratification in such cases. For patients at high risk, in whom an early (< 24 hours) invasive strategy is ideally indicated, the procedure may have to be delayed till SARS-CoV-2 test results are available [36].

In patients at intermediate risk, if any of the alternative diagnoses to type 1 MI seem plausible, such as Type II MI, myocarditis or stress cardiomyopathy, a non invasive strategy such as CCTA should be pursued. When infrastructure, catheterization laboratories or operators are not available owing to the high demand, non-invasive conservative management with early discharge from the hospital and planned clinical follow-up may have to be resorted to [36].

ST Elevation Myocardial Infarction (STEMI)

As reperfusion therapy should not be delayed in patients with STEMI, it may be safer to proceed with treatment assuming each patient to be COVID-19 positive until otherwise proven. All patients should undergo testing for SARS-CoV-2 as soon as possible following first medical contact irrespective of the reperfusion strategy. Primary PCI remains the reperfusion therapy of choice if feasible within the recommended time frame (i.e., maximum delay from STEMI diagnosis to reperfusion of 120 minutes) without compromising the safety of HCP and other patients. If the target time cannot be met and fibrinolysis is not contraindicated, fibrinolysis should be done immediately [36].

A suggestion has been made to perform left ventriculography during cardiac catheterization to reduce the need for echocardiography. PCI of non-culprit lesions should be considered during the same hospitalization in the presence of persistent symptomatic ischaemia, subocclusive stenoses, and/or angiographically unstable lesions. Treatment of other lesions may be delayed [36].

HEART FAILURE (HF)

Data on acute HF in COVID-19 are scarce. In one report, 23% of all hospitalized patients developed HF. HF prevalence was significantly higher in fatal cases compared with survivors (52% vs. 12%, $p < 0.0001$) [72]. The mechanisms of acute HF complicating the clinical course of COVID-19 include acute myocardial ischaemia, infarction or inflammation (myocarditis), stress-induced cardiomyopathy, ARDS, acute kidney injury and hypervolaemia, cytokine storm, and sustained or repetitive tachyarrhythmia. Hypoxaemia, dehydration and hypoperfusion may contribute to worsening haemodynamic status.

Myocarditis should be suspected in COVID-19 patients with acute HF or cardiogenic shock without preexisting CV disorder. Significantly elevated BNP/NT-proBNP levels indicate acute HF. CCTA is preferred to rule out concomitant CAD. CMR may be used for further diagnostic assessment. Endomyocardial biopsy is not recommended [36].

The treatment strategy for acute HF remains the same in patients with and without COVID-19. There are no recommendations specific for the treatment of SARS-CoV-2-associated myocarditis. Successful recovery of a patient with fulminant myocarditis has been reported with high-dose parenteral glucocorticoid therapy and immunoglobulin, along with other therapeutic measures [27].

ACUTE PULMONARY EMBOLISM

In the absence of contraindications, anticoagulation at standard prophylactic doses should be considered in all patients admitted with COVID-19 infection [73,74]. The specificity of D-dimer tests may be lower in this setting, as patients with COVID-19 have been shown to have higher levels of D-dimer, Fibrin Degradation Products (FDP), and fibrinogen, compared with healthy controls [75].

When acute PE is confirmed, treatment strategy is guided by risk stratification in accordance with the existing guidelines [76]. Patients in shock should receive immediate reperfusion therapy. Haemodynamically stable patients should receive therapeutic anticoagulation with either Unfractionated Heparin (UFH), Low Molecular Weight Heparin (LMWH) or a non-vitamin K Antagonist Oral Anticoagulant (NOAC). It is to be remembered that NOACs may have interactions with some of the investigational drugs for COVID-19, notably ribavirin and lopinavir/ritonavir, warranting their avoidance in such cases.

ARRHYTHMIAS

The treatment of cardiac arrhythmias is not significantly different in these patients and should be in concurrence with the current guidelines. Optimization of electrolytes, modification of drugs and ECG monitoring for prolonged QTc interval should be given ample importance. The possibility of drug interactions involving antiviral, antiarrhythmic and anticoagulant drugs should be considered. Administration of QT interval (QT) prolonging drugs (hydroxychloroquine and azithromycin) in the setting of antiarrhythmic drug therapy, dyselectrolytemia, renal dysfunction,

and/or bradycardia has the potential to precipitate Torsades de Pointes. Risk calculators are available for identification of patients at a high risk for ventricular arrhythmia.

Strategies for prevention of drug-induced pro-arrhythmias include the following [36]:

1) Identification of risk factors for QTc prolongation (Table 2) and correction of modifiable risk factors (for example, serum potassium should be kept at high normal levels (≥ 4.5 mEq/L) [77]

2) Risk assessment with baseline ECG: QTc ≥ 500 ms entails risk of developing TdP or sudden death

3) Follow-up ECG while on treatment: QTc ≥ 500 ms or ΔQTc ≥ 60 ms warrants consideration of switching to a drug with a lower risk of QTc prolongation or reducing the dose

4) Since bradycardia prolongs QT and facilitates TdP, extreme care is warranted during concomitant use of beta-blockers, CCBs, ivabradine and digoxin

Although intravenous Amiodarone is the antiarrhythmic drug of choice in critically ill patients with recurrent VT/VF or AF/atrial flutter, its combination with hydroxychloroquine and azithromycin should preferably be avoided. Discontinuation of background antiarrhythmic drug therapy and initiation of rate control drugs may be considered in haemodynamically stable patients with AF/atrial flutter, to avoid interaction with COVID-19 treatment. The therapeutic options may be re-assessed after recovery from the viral infection [36].

Table 2: Risk factors for QTc prolongation.

Non-modifiable	Modifiable
Congenital LQTS	Hypocalcaemia
Female sex	Hypokalaemia
Age > 65 years	Hypomagnesaemia
Structural heart disease	Concomitant use of QTc-prolonging medications
Renal or hepatic impairment	Bradycardia

Elective electrophysiologic procedures such as ablation and cardiac device implantation should be postponed, and pharmacological treatment options should be utilized to the maximum. Remote monitoring may be utilized as much as possible for follow up of patients with implantable cardiac devices [36].

SAFETY PRECAUTIONS IN CATHETERIZATION LABORATORY

It is reasonable to regard all patients as possible SARS-CoV-2 positive, particularly in regions with high rates of community transmission. No patient entering the catheterization laboratory (cath lab) should be without a surgical mask. When there are two negative results within 48 hours in the absence of symptoms of virus infection, invasive coronary procedures may be performed in a cath lab reserved for SARS-CoV-2-negative patients [36]. Emergency invasive procedures in patients whose SARS-CoV-2 results are either awaited or have come positive should ideally be performed in a COVID-19 dedicated cath lab if available.

Patients with borderline respiratory status should be intubated prior to shifting to the cath lab to avoid emergent intubation and aerosol generation in the lab. The number of staff in the cath lab should be minimized. The number of operators should be limited to the essential, especially in the electrophysiology laboratory. HCP should be well-versed in proper techniques for donning and doffing PPE. While dealing with haemodynamically unstable patients, HCP should wear Level II or Level III PPE, including gown, gloves, goggles, and a FFP2/FFP3 mask [36].

Powered Air-Purifying Respirator (PAPR) systems reduce the risk of aerosol dispersion during suctioning, intubation etc. High-efficiency particulate air filter may be placed between the endotracheal tube and the ambu-bag valve to reduce the risk of aerosol dispersion during manual ventilation. Terminal cleaning and sanitization of the lab should be performed after each procedure, and air exchange times of the lab must be ensured to be in the range of 15-30 exchanges per hour [36].

FUTURE PERSPECTIVES: LONG TERM CARDIAC SEQUELAE (POST–COVID-19 CARDIAC SYNDROME)

Although the higher morbidity and mortality associated with acute cardiac injury in patients with COVID-19 has been established, the impact on convalescent phase or long-term cardiac recovery is unknown. It is well known that viral myocarditis can evolve into overt or subclinical myocardial dysfunction, and risk of complications including sudden death looms in the convalescent phase of viral myocarditis. This raises the possibility that patients recovering from COVID-19 may still be at risk of cardiomyopathy, coronary artery disease, atrial fibrillation, or ventricular arrhythmias [78].

In a small study of recovered patients with ongoing cardiac symptoms, Cardiovascular Magnetic Resonance (CMR) imaging revealed cardiac involvement in 58% of patients consisting of myocardial edema and scar by Late Gadolinium Enhancement (LGE) [79]. In the most recently published German study on 100 patients recently recovered from COVID-19 infection, CMR revealed cardiac involvement in 78 patients (78%) and ongoing myocardial inflammation in 60 patients (60%), independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis. These findings indicate the need for screening for residual cardiac involvement in the convalescent phase as well as long-term cardiovascular consequences of COVID-19 [80].

The long term effects of acute phase treatment including antifibrotic therapy, anti-inflammatory therapy, cell-based therapy, or antiviral therapy need to be determined. The optimal screening strategy for post COVID-19 cardiac dysfunction is unknown at present. One suggestion is to define the population at highest risk by identifying those with elevated hs-cTn and/or brain natriuretic peptide levels, and follow them up for long-term cardiac sequelae of COVID-19 [78].

CONCLUSION

The impact of COVID-19 in the practice of cardiology extends beyond the clinical Cardiovascular (CV) manifestations of the disease. Many treatment modalities used in the treatment of COVID-19 have direct or indirect relevance to the CV system. Management of CV disease in patients with proven or suspected COVID-19 infection warrants modification of existing practices and guidelines so as to suit the changed health care environment. Long-term cardiovascular consequences of COVID-19 need to be determined with appropriate follow-up of patients recovering from the infection.

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