COVID-19 and myocardial injury

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ABSTRACT

The 2019 coronavirus pandemic (COVID-19), caused by SARS-CoV-2, has affected millions globally and has accounted for a multitude of deaths. Cardiovascular involvement with myocardial injury is common and is associated with severe morbidity and mortality. The pathophysiology of acute myocardial injury is complex and may include type I and type II myocardial infarction, direct damage to the cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, interferon mediated immune response, exaggerated cytokine response by Type 1 and 2 helper T cells, in addition to hypoxia. Angiotensin converting enzyme-2 receptors (ACE2-R) play a pivotal role in mediating viral entry into cells. Disruption of receptor signalling may also be the principal mechanism facilitating viral pathogenicity and altered ACE2-R biology may be a reason why patients with cardiovascular disease are more likely to be infected with SARS-CoV-2 and more likely to develop severe symptoms. New-onset hypertension, arrhythmia, myocarditis, heart failure, cardiomyopathy and coronary heart disease are among major cardiovascular disease comorbidities and complications seen in severe cases of COVID-19. As a surrogate for myocardial injury, multiple studies have shown increased cardiac biomarkers, mainly cardiac troponins I and T, in the infected patients – especially those with severe disease. Myocarditis is another cause of morbidity among COVID-19 patients. SAHeart 2020;17:330-337

INTRODUCTION

The 2019 coronavirus disease (COVID-19), caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), has infected millions of individuals globally, accounting for over a million deaths directly attributable to infections. Countless other lives have been altered or shortened as a result of the multiple and pervasive indirect effects of the pandemic. While much of the focus has been on pulmonary infection and managing its more severe complications, it has become clear that SARS-CoV-2 can result in severe systemic inflammation and involve most organ systems.

The heart has emerged as a primary site of infection, with evidence of direct viral replication and viral cytopathy in cardiomyocytes, fibroblasts, endothelial cells and cardiac interstitial cells.[1,2] It is clear that the cardiovascular system plays key roles in determining severity of SARS-CoV-2 disease. First, the cell-surface receptor mediating viral entry into cells is highly expressed in cardiovascular tissue.[3] Second, patients with pre-existing cardiovascular conditions are at considerably greater risk of developing severe disease.[4] Finally, many hospitalised COVID-19 patients develop acute myocardial injury, and elevated biomarkers of this injury are strong predictors of poor outcomes.[5]

Yet, it is not clear how the three phenomena described above are interrelated. For instance, questions abound about whether elevation in serum biomarkers is causally linked with either viral trophism or with pre-existing cardiovascular disease (CVD). There is, however, increasing evidence that there are several distinct causes of acute myocardial injury in COVID-19, and that more than one cause may be present in the same patient at the same time or during different disease phases.[6] A better understanding of which patients are at greatest risk and identifying modifiable cause(s) of myocardial injury, may have direct practical applications for improved management of patients with COVID-19.

The link between coronaviruses and CVD is not new. Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV have both been linked with acute myocardial injury associated with clinical phenotypes of myocarditis, acute heart failure, left ventricular (LV) systolic dysfunction, arrhythmia and plaque rupture.[7-10] Similarly, there are multiple recent reports of SARS-CoV-2 causing new-onset hypertension, arrhythmia, heart failure, myocarditis, myocardial infarction (MI) and Takotsubo.[11-17] In addition, even in the absence of these clinical phenotypes, patients experiencing myocardial injury from SARS-CoV-2 have a significantly higher risk of in-hospital mortality.[5,18] Given our rapidly evolving understanding of cardiovascular involvement in patients with COVID-19, we thought it timely to place into context the growing evidence for the epidemiology, disease mechanisms and outcomes of myocardial injury from SARS-CoV-2 infection.

EPIDEMIOLOGICAL CONSIDERATIONS

The clinical presentation of COVID-19-associated myocardial involvement varies between geographical locations. Reportedly, frequent presentations in South Africa involve chest pain and symptoms of heart failure, whereas in the United Kingdom, for example, patients mainly present with thrombotic myocardial infarction initially. Many South African patients present with new-onset heart failure, but LV ejection fraction is often preserved. Furthermore, genetic factors may play a role in disease severity: Black and Asian ethnicity appears to be associated with a more severe disease course, with more than fourfold risk of death in these ethnic groups in the United Kingdom.

COVID-19 AND ACUTE MYOCARDIAL INJURY

Following recommendations from the Task Force for the Fourth Universal Definition of Myocardial Infarction, the term myocardial injury (acute or chronic) applies to any patient in whom at least one cardiac troponin (cTn) concentration is above the 99th percentile upper reference limit (URL).[19] Myocardial injury is considered acute if there is a rise and/or a fall of cTn values. Cardiac troponin I (cTnI) and T (cTnT) are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart. Increases in cTnI values have not been reported to occur following injury to non-cardiac tissues, whereas cTnT may be elevated following injury to skeletal muscle. Myocardial injury is commonly encountered clinically and is associated with an adverse prognosis.[19-21] While myocardial injury is a prerequisite for the diagnosis of MI, it is also an independent entity. To establish a diagnosis of MI, criteria in addition to abnormal biomarkers are required. Non-ischaemic myocardial injury may arise secondary to many cardiac conditions such as myocarditis or may be associated with non-cardiac conditions such as renal failure or pulmonary embolism (Table 1).

Myocardial injury is common in patients with COVID-19. Incidence of myocardial injury from COVID-19 is unclear due to variations in cTn assays, diagnostic thresholds, populations studied and timing of samples in relation to disease onset.[22] High-sensitivity cTn assays, particularly in patients with greater clinical severity, are likely to yield higher values.[5,18,22,23] Patients with myocardial injury should be classified as: (i) chronic myocardial injury, (ii) acute non-ischemic myocardial injury, or (iii) acute myocardial infarction (MI);[24] all of which are associated with increased mortality.[25]

Acute non-ischaemic myocardial injury, in patients with dynamic rising and/or falling cTn concentration without clinical evidence of myocardial ischaemia, is probably the predominant mechanism for cTn increases in patients with COVID-19.[24] Despite emerging reports of myocarditis in patients with COVID-19, cTn increases will not always be due to myocarditis: clinical context, pre-test probability, and careful clinical evaluation should inform the nature of cTn increases. Acute MI is increased in COVID-19 due to increased inflammatory, prothrombotic, and procoagulant responses. Data from several COVID-19 studies confirm that this is also the case for COVID-19.[26,27] Conceptually, the risk for type 2 MI is higher because of the respiratory failure with hypoxia and haemodynamic disturbances that occur in COVID-19 with severe illness.

Chronic cardiovascular disease and COVID-19

In one of the earliest reports of patients who died from COVID-19 in Wuhan, important comorbidities included hypertension (20%), diabetes (15%) and CVD (15%).[15] Chronic myocardial injury is reported to be associated with established CVD and with disease severity.[12,15,28,29] While the overall case fatality rate of COVID-19 reported by the Chinese Centre for Disease Control and Prevention is 2.3%, the individual case fatality rate of patients with CVD is 10.5% [highest among those with any comorbidities, including chronic respiratory disease (6.3%), cancer (5.6%), diabetes (7.3%) and hypertension (6.0%)].[30]

Acute non-ischaemic myocardial injury and COVID-19

Acute LV dysfunction is not a common sequela of COVID-19.[31] SARS-CoV-2 infection is associated with acute elevations in

TABLE I: Aetiologies of myocardial injury.

Myocardial injury related to acute myocardial ischaemia	Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance	Other causes of myocardial injury
Atherosclerotic plaque disruption with thrombosis	A. Reduced myocardial perfusion • Coronary artery spasm • Microvascular dysfunction • Coronary embolism • Coronary artery dissection • Sustained bradyarrhythmia • Hypotension or shock • Respiratory failure • Severe anaemia	A. Cardiac conditions • Heart failure • Myocarditis • Cardiomyopathy • Takotsubo • Coronary revascularisation procedure • Cardiac procedure other than revascularisation • Catheter ablation • Defibrillator shocks • Cardiac contusion
	B. Increased myocardial oxygen demand • Sustained tachyarrhythmia • Severe hypertension with or without left ventricular hypertrophy	B. Systemic conditions • Sepsis or infectious disease • Chronic kidney disease • Stroke, subarachnoid haemorrhage • Pulmonary embolism, pulmonary hypertension • Infiltrative disease • Chemotherapy • Critically ill patients • Strenuous exercise

Adapted from Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J 2019;40:237-269.

NT-proBNP, cTnI and hs-CRP, which are markers of myocardial injury and inflammation, respectively.(32) In addition, elevated cardiac biomarkers were significantly correlated with severe disease and critical illness. Age, male sex, elevated serum creatinine, hypertension, and coronary artery disease were additional factors contributing to disease severity.(32) Elevations in hs-cTnI were associated with admission to the intensive care unit (ICU).(18) Similarly, in COVID-19 patients who required ICU admission, levels of creatine kinase (CK)-MB and hs-cTnI were significantly higher.(28) A Chinese case series of 187 patients with confirmed cases of COVID-19, reported a third to have elevated cTnT levels consistent with myocardial injury; this group had higher mortality.(25)

Myocarditis is a specific clinical complication of acute non-ischaemic myocardial damage and can be diagnosed histologically following endomyocardial biopsy (EMB), on imaging using cardiovascular magnetic resonance (CMR) – Figure 1 – or clinically. Viral infection is often noted to be a common cause of myocarditis. While fulminant myocarditis has been described to be associated with COVID-19, most reported cases in the literature report a chronic lymphocyte dominant myocarditis following SARS-CoV-2 infection.(1,15,16,30,33-35) In a multicentred study of 84 patients with COVID-19, 15.5% had abnormal electrocardiograms and elevated cardiac enzymes; however, only 5% were clinically diagnosed with myocarditis.(36,37) Finally, increased levels of N-terminal pro B-type natriuretic peptide and cTnI were reported in 27.5% and 10% of patients, respectively; IL-6 and other inflammatory cytokines were elevated in patients who experienced a more severe disease course requiring ICU admission, leading the authors to postulate that elevated cytokines were due to cytokine storm, attributed as the cause of fulminant myocarditis in these patients.(33)

Delayed multisystem inflammatory syndrome in children

A systemic inflammatory response syndrome with severe acute myocardial injury and dysfunction that affects children has been reported by several groups.(38-40) Notably, this "Kawasaki-like" syndrome has a delayed-onset following COVID-19. When ethnic origins were reported, early reports from European centres indicated a striking association with sub-Saharan black ancestry.(40,41) In these reports, the often-severe systolic impairment appeared rapidly reversible following treatment with intravenous immunoglobulins (and/or steroids). Diagnosis of COVID-19 was made through detection of SARS-CoV-2 antibodies in the majority of children (82% of 55 cases),(38,39) but PCR testing was positive in only a minority (38% of 63 cases).(38-40) Of note, co-existence of IgM, IgG and IgA in most children, is consistent with isotype switching occurring several weeks after initial viral exposure.(39) Mechanisms that underlie this delayed presentation are presumed to be immunobiological, and it remains possible that the cardiac involvement in some adults may follow similar patterns.

Acute myocardial infarction and COVID-19

While primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients presenting with acute MI, its success depends on rapid achievement of procedure completion from symptom onset, ideally within 90 to 120 minutes.[42] In patients with chest pain syndromes presenting for care, the ideal time frame of <120 minutes has been altered during the coronavirus pandemic for several reasons: delayed or refused transfers for bed capacity, lack of early cardiac catheterisation laboratory activation, delays in preparation due to personal protective equipment, and COVID-19-related misleading clinical presentations.[43] Delays in seeking medical care in a small cohort of STEMI patients, with a median time of 318 minutes from onset of symptoms to first medical contact, was described in Hong Kong, and associated with poor outcome.[43] During the pandemic, there have been numerous reports of diminished numbers of patients presenting with acute coronary syndromes. Analysis from 9 high-volume hospitals in the United States reported an estimated 38% reduction in cardiac catheterisation laboratory STEMI activations, similar to the 40% reduction noted in Spain.[44,45]

PATHOPHYSIOLOGY OF MYOCARDIAL INJURY IN COVID-19

Pathophysiological mechanisms underlying myocardial injury caused by COVID-19 are manifold, with varying amounts of evidence for different theories. Figure 2 summarises the postulated mechanisms. Human SARS-CoV-2 infection of the myocardium is dependent on ACE2 receptors. Disruption of ACE-2 leads to cardiomyopathy, LV dysfunction, and heart failure.[46] Detrimental ACE2 down-regulation limits cardioprotective effects of angiotensin 1 - 7, leading to increased tumour necrosis factor alpha (TNFα) production. In COVID-19, elevated TNFα in patients with underlying CVD was associated with poor outcomes, supporting the idea of severe inflammatory response as a possible mediator of cardiomyocyte damage.[5] There is increasing evidence of direct viral damage to the cardiomyocytes, systemic inflammation, endothelial shedding, cytokine-induced myocardial injury, myocardial interstitial fibrosis, interferon mediated immune response, exaggerated cytokine response by Type 1 and 2 helper T cells, electrolyte imbalances, in addition to coronary plaque destabilisation and hypoxia (Figure 3).[2,25,47-49] Swift development of innate immunity is important for early clearance of the virus. Delayed innate immunity and subsequent activation of adaptive immunity is an important determinant of severe myocardial disease and chronic myocardial inflammation (Figure 4).[50]

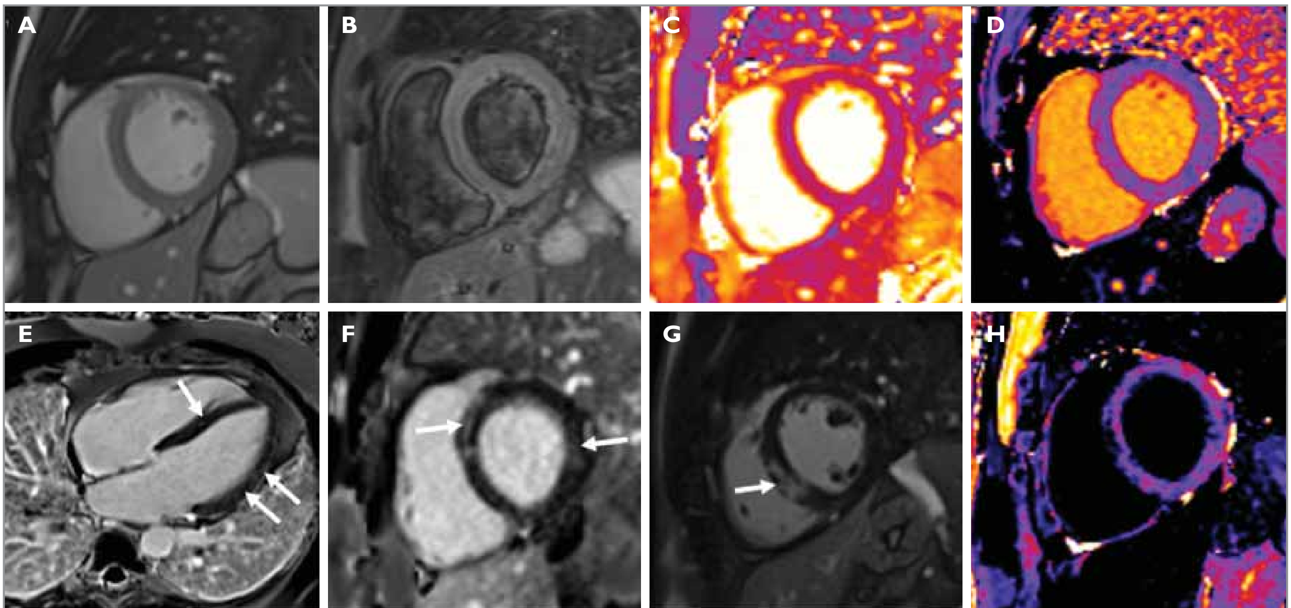

FIGURE 1: Cardiovascular magnetic resonance in a patient with COVID-19 myocarditis.
Patient treated for COVID-19 six weeks prior, with low positive cTn. Referred for CMR for evaluation of cause for persistent shortness of breath and palpitations. A: Steady-state free precession cine short axis view; B: Short-Tau inversion recovery imaging showing evidence of myocardial oedema with signal intensity ratio of 2 between myocardium and remote skeletal muscle; C: T2 map confirming myocardial oedema (T2 = 53 ms); D: T1 map at 1.5 Tesla with elevated T1 time (1019 ms); E: Phase-sensitive inversion recovery (PSIR) horizontal long axis image showing mid-wall enhancement in the septum and subepicardial enhancement in the inferolateral wall; F: PSIR basal short-axis image with mid-wall enhancement in the septum and subepicardial enhancement in the lateral wall; G: PSIR short-axis image at mid-ventricular level showing more confluent mid-wall enhancement; and H, postcontrast T1 map with elevated calculated extracellular volume of 32%.

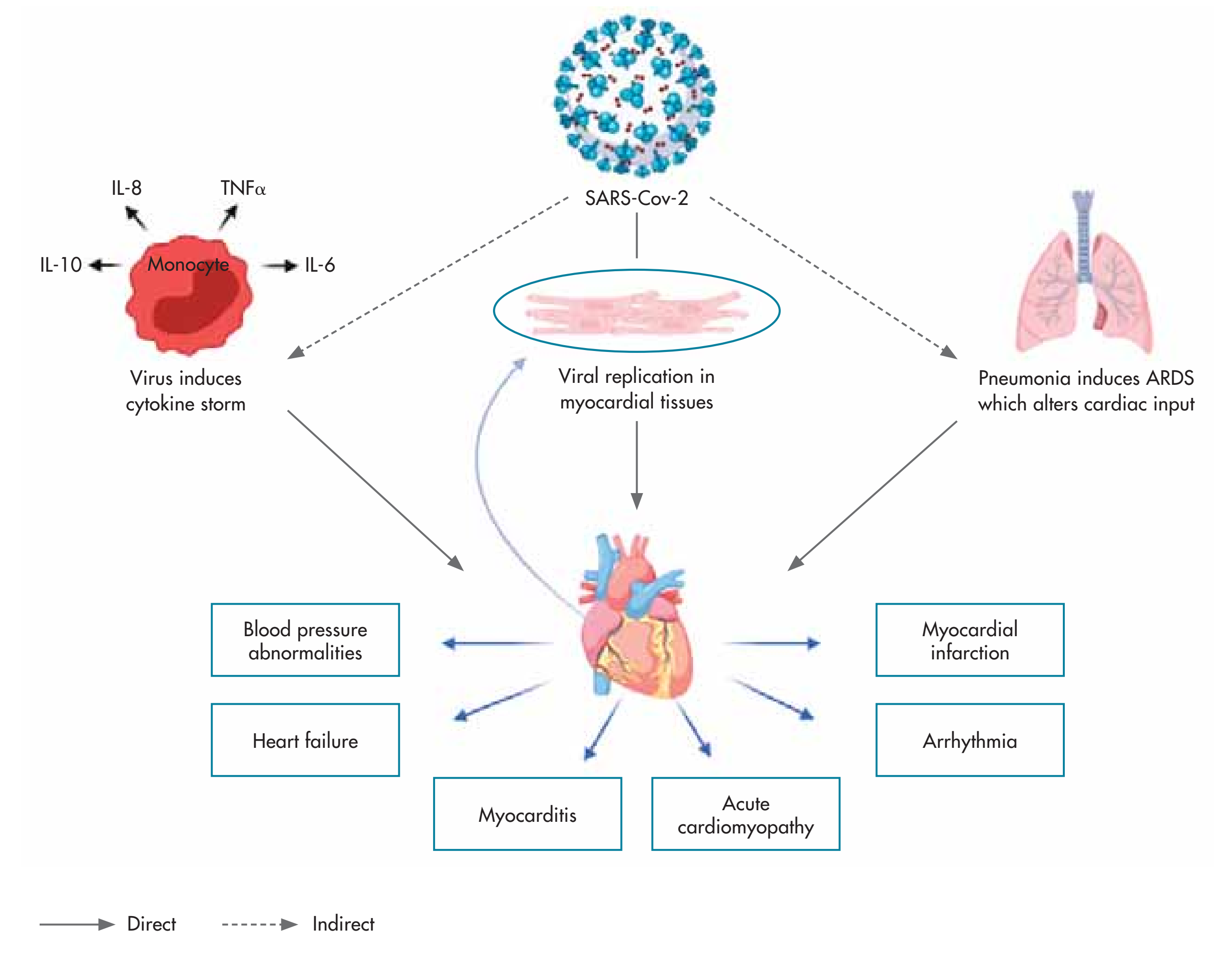

FIGURE 2: Mechanisms of myocardial injury in COVID-19.

Infection with SARS-CoV-2 is characterised by a rapid reduction in T lymphocytes (both CD4+ and CD8+) in the peripheral blood, which precedes the development of symptoms and radiological abnormalities.[50,51] Despite the reduction in lymphocytes, there is a frequent activation of adaptive immunity characterised by highly proinflammatory CCR6+ Th17 CD4+ cells and increased cytotoxic granules in CD8+ T cells (perforin positive, granulysin positive and granulysin/perforin double-positive).[51] In addition, abnormalities in T regulatory cells have been reported in cases of severe CVD.[52] CD4+ T cells appear to play a central role in host-immune defence against SARS-CoV-2 infections.[53] In acute respiratory distress syndrome and in those with a cytokine storm, increased levels of TNF-α, IFN-γ, inducible protein 10, IL-6, and IL-8 are elevated and thought to contribute to tissue destruction.[54]

CARDIOVASCULAR MANIFESTATIONS OF MYOCARDIAL INJURY

Elevated cTn is frequently observed and reflects myocardial injury related to COVID-19. In patients with severe and fatal COVID-19, higher levels of cTn (>5xULN) were associated with severe respiratory failure, tachycardia, systemic hypoxaemia, myocardial injury either from direct or indirect viral myocarditis, endothelial dysfunction or plaque rupture triggered by COVID-19 with subsequent acute coronary syndrome, Takotsubo or progression to multiple organ failure.[55] High BNP/NT-proBNP levels, seen in severe disease, correlate with right ventricular stress. Elevated D-dimers are associated with poor outcome; elevated D-dimers on admission correlated with COVID-19 in-hospital mortality.[18,56]

Incidence of myocarditis in COVID-19 is unclear, as the spectrum of symptoms varies from mild symptoms such as chest

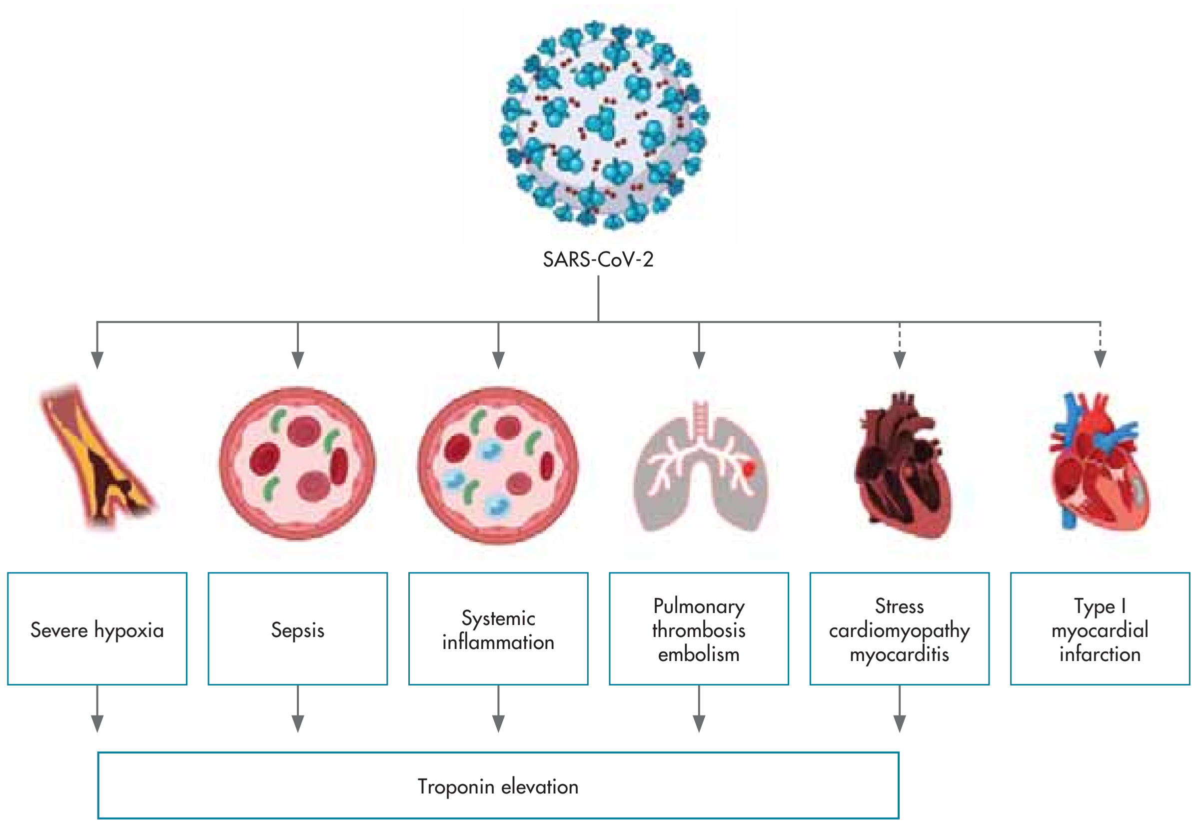

FIGURE 3: Phenotypes of myocardial injury in COVID-19.

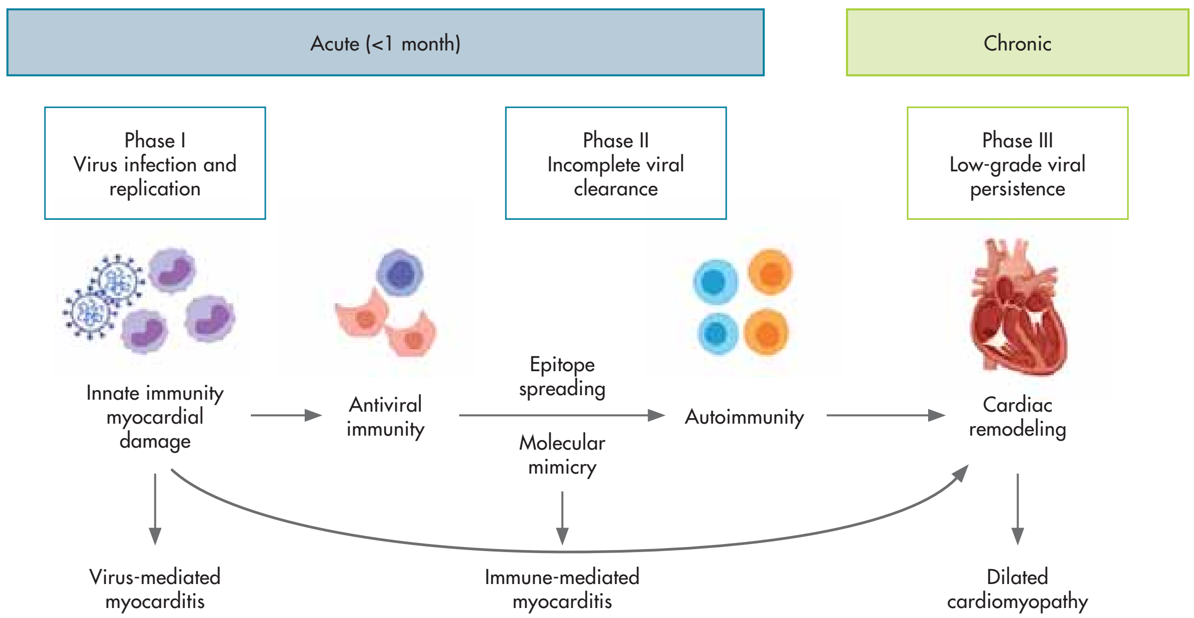

FIGURE 4: Immunological basis and disease phases of myocardial injury in COVID-19.

pain, dyspnoea and fatigue to severe features like biventricular failure, cardiogenic shock, arrhythmia, and sudden cardiac death. COVID-19 myocarditis is due to a combination of direct cell injury and T-lymphocyte-mediated cytotoxicity augmented by the cytokine storm.[33] COVID-19-induced myocarditis may mimic an acute coronary syndrome with ST segment elevation.[18]

Commonly reported arrhythmias in COVID-19 are atrial fibrillation, supraventricular tachycardia and ventricular tachycardia (VT); these may occur in the setting of myocarditis, MI and in critically ill patients with hypoxia and shock.[57] Bradycardia has rarely been reported. Other mechanisms for arrhythmias include electrolyte disturbance (mainly hypokalemia), and cardiotoxic therapies (e.g. chloroquine/hydroxychloroquine and azithromycin) that prolong QT interval with potential development of polymorphic (VT) and fever, which may unmask channelopathies such as Brugada syndrome and long QT syndrome.

LV systolic dysfunction, acute heart failure, and cardiogenic shock are commonly reported in COVID-19, but incidence of heart failure is undetermined, and reported to be 52% of deceased patients and 12% in discharged patients.[12] EMB in patients with COVID-19 reveals intracardiomyocyte virus particles.[2,23]

CONCLUSIONS

SARS-CoV-2 is a global health crisis, with strong predilection for cardiovascular involvement and myocardial injury. Patterns of injury include chronic myocardial injury, acute non-ischaemic myocardial injury and acute (type 1) MI. Mechanisms of cardiac damage are numerous and include direct insult to myocytes by the virus, cytokine and interferon inflammatory responses, myocardial interstitial fibrotic response, and T1 and T2 helper cell response. Better diagnostic tools and registry data are needed for further characterisation of mechanisms of SARS-CoV-2-related myocardial injury and to help guide development of management strategies. At present, there is no specific treatment for COVID-19 myocardial injury.

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