Chapter 10
Cardiomyopathy in COVID-19 (Epidemiology, Influence on Prognosis, Pathogenesis, Treatment)

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Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The pathophysiology of SARS-CoV-2 is characterized by overproduction of inflammatory cytokines leading to systemic inflammation and multiple organ dysfunction syndrome, acutely affecting the cardiovascular system [1]. The mechanisms of cardiovascular injury caused by SARS-CoV-2 infection have not been fully elucidated, but it is speculated that SARS-CoV-2 affects the cardiovascular system through multiple mechanisms, including direct injury, downregulation of angiotensin-converting enzyme 2 (ACE2), immune injury, hypoxia injury, and psychological injury. Cardiac injury with troponin increase, significantly related to inflammation biomarkers, illustrate a relevant correlation between myocardial injury and inflammatory hyperactivity triggered by viral infection [2]. The SARS-CoV-2 infection occurs through the coupling of S-protein located on the surface of the virus with ACE2, which acts as a receptor for the virus. ACE2 is mostly present in the lungs and seems to be the main gateway for the virus. It is also present in the heart, which can lead to complications [2]. Cardiovascular implications result in a worse prognosis COVID-19 patients,

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emphasizing the importance of precocious detection and implementation of optimal therapeutic strategies. Patients with previously established comorbidities such as cardiovascular diseases are at a particularly high risk of morbidity and mortality from this viral infection. Cardiac injury in patients infected with the novel Coronavirus seems to be associated with higher morbimortality [3]. Moreover, several studies showed that COVID-19 can aggravate pre-existing cardiovascular disease and cause new cardiovascular injuries [3]. It is important to identify cardiac-related manifestations in patients with COVID-19.

The clinical manifestations of cardiac involvement could range from an absolute lack of symptoms in the presence of increased troponin levels, with or without ECG or imaging abnormalities, to arrhythmia and sudden cardiac death, pulmonary embolism, acute coronary syndromes, myocarditis, acute heart failure, and cardiogenic shock [4].

Heart Failure, Cardiomyopathies and COVID-19

The link between COVID-19 and heart failure (HF) is intricate. During the pandemic period the reduction of HF hospitalizations is observed due to patient fear and lack of free hospital possibly leading to an increase in HF mortality. The history of HF is a risk factor for a more severe clinical course of COVID-19 [5] and on the other hand HF can be a consequence of COVID-19-related myocardial damage—Fig. 10.1. HF patients were more prone to develop myocardial injury [4, 5].

In a prospective cohort study, among 5279 people with laboratory confirmed SARS-CoV-2 infection, more than a half were admitted to hospital, of whom 1904

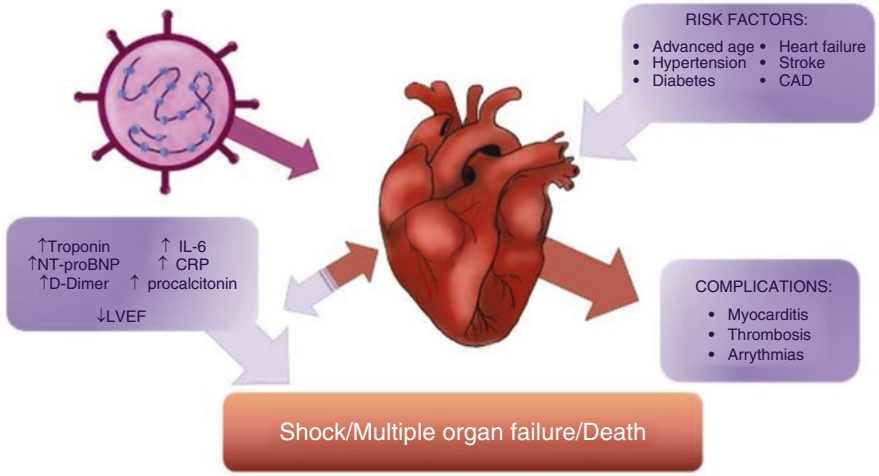

Fig. 10.1 The influence of SARS-CoV-2 on myocardial injury

(69.5%) were discharged alive [5]. In this analysis the strongest risks for critical illness besides age were associated with heart failure (1.9, 1.4 to 2.5), BMI >40 (1.5, 1.0 to 2.2), and male sex (1.5, 1.3 to 1.8) [5]. A clinical study of 99 cases with confirmed COVID-19 from Wuhan showed that 11 (11%) patients had died of which two patients had no previous history of chronic heart disease but developed heart failure and eventually died of a sudden cardiac arrest [6]. Additionally, Chen et al. [7] reported that cardiac complications were observed more frequently in 113 deceased patients with COVID-19, including acute cardiac injury (72/94; 77%) and heart failure (41/83; 49%). New onset of HF was observed in as much as a quarter of hospitalized COVID-19 patients; and in as much as one-third of those admitted to the intensive care unit (ICU) [8], despite not having a history of HF. It was reported that in HF patients, monocytes seem to produce more TNF-α and less IL-10 than healthy subjects [9]. Heart failure in patients with COVID-19 occurs as a result of different myocardial aggression mechanisms such as direct myocardial injury by viral action, indirect and direct inflammatory damage, oxygen supply–demand imbalance, and increase of atherothrombotic events due to inflammatory destabilization of atheromatous plaques resulting in acute myocardial dysfunction [10].

In COVID-19 patients presenting acute HF, left ventricle (LV) systolic function is not usually compromised; on the contrary, impairment of right ventricular (RV) systolic function and LV diastolic function can be found [11]. Out of 100 patients hospitalized for COVID-19, 32% were reported to have normal echocardiography, whereas 39% presented RV dilatation and dysfunction and 16% LV diastolic dysfunction, whereas reduced LV ejection fraction (EF) was reported only in <10% [12]. Similar results are described in a large international cohort study [4]. Accordingly, LV diastolic impairment with elevated LV filling pressures (E/e′ ratio) could be observed in a quarter of patients admitted for COVID-19.

Consistently, patients hospitalized with COVID-19 showed high likelihood of presence of HF with preserved ejection fraction (HFpEF) as compared with patients without COVID-19 according to the score of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), and HFpEF was found associated with cardiac structural and functional alterations and myocardial injury [13].

The persistent myocardial damage and fibrosis in the subacute and chronic phases after recovery suggest that COVID-19 may be an independent risk factor for the development of HF [14]. The early identification of patients with cardiac abnormalities is of pivotal importance as they may benefit from cardioprotective therapy and need different follow-up strategies. Heart failure is common and may be encountered de novo as part of the clinical course of COVID-19 or in those with pre-existing cardiac disease. It is thus imperative to understand the diverse interactions between this disease state and the virus to optimize the management of these patients.

In the study of Omidi et al. the authors aimed to describe the creation of systematic search in databases up to August 2020, for all relevant studies about COVID-19 and cardiomyopathies. A total of 29 articles with a total number of 1460 patients were included. Diabetes, hyperlipidemia, hypertension, ischemic heart disease, and

obesity were the most recorded comorbidities among patients with COVID-19 and cardiomyopathy. In the laboratory test, 21.47% of patients had increased levels of troponin. In addition, all of the patients had elevated D-dimer levels. Echocardiographic measurements showed mild, moderate, and severe left ventricular dysfunction present in 17.13%, 11.87%, and 10% of patients, respectively. In conclusion, cardiomyopathies were common disorders in patients with COVID-19 [15].

Stress-Induced Cardiomyopathy and COVID-19

Takotsubo syndrome (TTS) is a type of severe reversible cardiac disability. It is also known as stress-induced cardiomyopathy, broken heart syndrome or stunned myocardium [16, 17]. Leading symptom of TTS is pain localized in the chest with or without dyspnea [16] Characteristic feature of takotsubo syndrome is transient dysfunction of left ventricle (akinesia, dyskinesia or hypokinesia) and it is demonstrated as apical ballooned, midventricular, basal or focal abnormalities in contraction of myocardium. Usually the region of the wall motion abnormalities extends beyond the territory supplied by a single coronary artery [18].

Features that indicate Takotsubo syndrome are visible in electrocardiography. We can observe ST segment elevation/depression, T wave inversion or prolonged QTc [18]. Biochemical markers can be elevated. There is an increased level of troponin, creatine kinase, and brain natriuretic peptide [18]. Similar features can be present in the acute coronary artery, however, in TTS usually there are no presenting abnormalities within coronary arteries [18].

The pathogenesis of TTS is not well understood, there are many theories trying to explain the formation of this cardiomyopathy. Takotsubo syndrome may be caused by physical or emotional stress. There are speculation that increased the level of catecholamine (adrenaline, noradrenaline, and dopamine) might have an impact on the development of Takotsubo cardiomyopathy. High dose of epinephrine can cause switching Gs protein to Gi protein in B2-AR receptors. The result is a decreased level of cAMP inside the cell and it may lead to negative inotropic effect on contraction of myocardium [19]. Another theory is that superphysiological level of catecholamine might lead to increased expression of G protein coupled receptor kinase 2 (GRK2) and B-arrestin2. Those molecules cause desensitization of B1-AR and that can trigger decreased contraction of left ventricle. Both of those theories can explain the apical ballooned since there is a higher presentation of those receptors in the apical region. Also neurological disorders may cause this syndrome. For instance, transient ischemic attack/stroke, seizures or pheochromocytoma could be a trigger [18]. TTS without COVID-19 more often affects postmenopausal women. It might be due to the possible decreased estrogen level. Animal models show that estrogen can protect cardiomyocyte by a downregulation of adrenoreceptors, hypothalamo-sympathoadrenal axis, and a rise in the amount of atrial natriuretic peptide which decreases the load of ventricles.

Previous research showed that infection of SARS-CoV2 can contribute to injury of myocardium and may be associated with higher prevalence of TTS. Infection of SARS-CoV2 can be related with a higher plasma level of catecholamine. Excretion of those hormones is caused by infection and it is a prevention of decompensation. Moreover, patients with severe infection may get intravenous infusion of adrenaline or noradrenaline. Superphysiological level of catecholamine is one of the potential triggers of development of takotsubo syndrome. Catecholamine increases the myocardium's oxygen demand and induces contraction of a vessels [16]. During infection of SARS-CoV2 there is an increased secretion of IL-6, TNF-alfa, and other proinflammatory cytokines (cytokine storm) and it may be connected with higher level of catecholamine [16]. Another elevated biomarker in TTS is N-terminal pro-brain-type natriuretic peptide (NT-proBNP) which is secreted in a larger amount due to the increased ventricular wall stress. The TTS level of a NT-proBNP is correlated with the stage of disfunction of left ventricle [16]. Severe COVID-19 may activate hypothalamic-pituitary-adrenal axis which leads to increased level of ACTH and cortisol. Correlation between hypercortisolism and TTS is not well established. Cortisol may also increase secretion of catecholamine. TTS was noticed in a patient who presented higher level of cortisol [16]. Another theory why COVID-19 may be related with takotsubo syndrome is increased mental stress during quarantine or self-isolation. People who have quarantined have a greater risk of depression, stress, insomnia or anxiety [16].

In the study by Kamal Sharma et al. the correlation between COVID-19 and prevalence of TTS was assessed. TTS in COVID-19 equally concern males (45%) and females (55%) unlike TTS without COVID-19 (males—10.2%, females—89.8%). It may be due to the fact that males suffer more frequently from the infection of SARS-CoV2. There was a significant increase of morbidity in TTS during COVID-19 and these patients have longer hospitalization than in the pre-pandemic era (8 days vs. 4–5 days) [20].

A lot of patients with TTS apart from increase of proinflammatory cytokines had elevated C-reactive protein (CRP), and excessive number of D-dimer what suggested potential relation with decreased function of left ventricle level of D-dimer was also related with the severity of COVID-19 [20]. TTS patients with TTS and COVID-19 presented wall motion abnormalities of both ventricles, changes within ST segment and T wave. There were also present diffused PR intervals and prolonged QTc [20–22].

Sars-cov2 infection may be associated with an increased risk of thromboembolic complications. Study performed by Zhou et al. reported that treatment with heparin reduced 28-day mortality. Administration of anticoagulants should be consider in high-risk COVID-19 patients with TTS (older-aged group, reduced left ventricle effective fraction (LVEF)) [20].

In the study of Kamal Sharma et al. majority of TTS patients were discharged from hospital (74.1%) successfully, but part of them (10/23) developed one or more complication such as cardiogenic shock, atrial fibrillation, heart failure, supraventricular tachycardia, or biventricular heart failure [20]. Patients who developed cardiogenic shock had higher mortality rate 33.3% (2/6 mortality). Triggering factors

had an impact on course of TTS in COVID-19 patients. Patients with COVID-19 and TTS had a higher mortality rate (14.8%) than patients with COVID-19 with pre-existing disease of cardiovascular system without TTS (5.8%) [20].

All high-risk patients with COVID-19 should be diagnosed for TTS. Early detection of TTS may reduce mortality and complication of cardiovascular system. Adequate treatment should be considered with antiplatelet medication, statin, and beta-blockers if its required [20].

There are attempts to treat TTS with neurohormonal drugs. The treatment usually consists of beta-blockers or renin-angiotensin system inhibitors. But there is not any reliable evidence that using of beta-blockers would be effective in preventing the reoccurrence of TTS. Systemic reviews and research papers show that there is no correlation between recurrence of TTS and therapy with beta-blockers. Moreover 30% of 1750 patients in the International Takotsubo Registry study were treated with beta-blockers when they developed TTS. There are no evidence that beta-blockers decrease mortality within 1 year of using this drugs upon discharge after TTS admission. In retrospective analysis, which included 2672 patients, 423 of them where treated with beta-blockers within 2 days of diagnosis of TTS and there was no noticeable change in 30-day in hospital mortality [23].

Information about using renin-angiotensin system inhibitors are inconclusive. The International Takotsubo Registry study reported that there is a correlation between using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and improvement in survival at 1 year. Subsequent Mayo Clinic study of 265 patients with TTS reported that after receiving an angiotensin-converting enzyme inhibitor at discharge, there was no improvement in the 1-year survival [23]. Clinical benefits of using beta-blocker have not been demonstrated, but treatment with ACE-1 could have an impact on ventricular remodeling and improve survival in 1 year [24]. Case-control study of 6000 patients did not found any connection between using ACE-1 and COVID-19. Therefore current protocols recommended continuing treatment with ACE-1 in patients infected by COVID-19 if they did not have other contraindications [24].

Dilated Cardiomyopathy and COVID-19

Dilated cardiomyopathy (DCM) is characterized by left ventricular dilation that is associated with systolic dysfunction. It is postulated that persistent immune activation upon viral infection increases the risk of developing dilated cardiomyopathy in COVID-19 patients [25]. Genetic inheritance arises in 30–48% of patients, and inflammatory disorders such as myocarditis or toxic effects from medications, alcohol, or illicit drugs also result in dilated cardiomyopathy. Viral infection is a known secondary cause of DCM [25].

There are several described case reports presenting de novo dilated cardiomyopathy in children with COVID 19 [26, 27] with significant reduction of ejection fractions and episodes decompensated heart failure.

In patients whose blood troponin levels are elevated after SARS-CoV-2 infection, long-term careful monitoring of cardiac function is necessary after recovery. Furthermore, studies should address whether conditions such as dilated cardiomyopathy would develop following COVID-19 even when patients are asymptomatic.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorder and is characterized by cardiac hypertrophy, left ventricular outflow obstruction in the majority of cases, and diastolic dysfunction [28].

In the study of Arabadijan et al. the clinical course and outcomes of COVID-19 in patients with HCM were analyzed [28]. The hospital admission rate was high at 20%. The case fatality rate in this sample was similar to the general population. Both individuals who died had multiple co-morbid conditions associated with higher morbidity and mortality. Among hospitalized patients, the distribution of non-obstructive and obstructive HCM patients mirrors the distribution in unselected HCM cohorts [29]. There were no significant differences in demographics, HCM characteristics, or COVID-19 risk factors between the hospitalized and not hospitalized group. Prior reports have noted that there is ACE2 receptor upregulation in HCM tissue specimens [30].

Another study examined cardiac samples from individuals with dilated cardiomyopathy, hypertrophic cardiomyopathy, and healthy controls, which also supported upregulation of ACE2 in HCM tissue, but did not observe a difference in ACE2 expression between HCM patients taking ACE inhibitor medicines and those who did not [31]. However, the clinical impact of this upregulation in HCM is unclear. Data presented above suggest that HCM in itself does not carry a higher risk of COVID-19 disease severity and complications. Established risk factors for severe COVID-19, such as age and obesity may be more prominent in this patients population.

Restrictive Cardiomyopathy and Arrhythmogenic Right Ventricular Cardiomyopathy in COVID-19

The number of data regarding restrictive cardiomyopathy (RCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) are scarce. RCM is characterized by diastolic dysfunction of a non-dilated ventricle. Multiple types of restrictive cardiomyopathies exist and vary in their pathogenesis, clinical presentation, diagnostic evaluation, treatment, and prognosis. Most restrictive cardiomyopathies are due to infiltration of abnormal substances between myocytes, storage of abnormal metabolic products within myocytes, or fibrotic injury [32].

In the study of Yildirim et al. the authors described a case of a 7-year-old female suffering from RCM infected with COVID-19 whose inotropic support and CPAP needed [32].

ARVC is characterized by progressive fibrofatty replacement of the myocardium that predisposes to ventricular tachycardia and sudden death in young individuals and athletes. It primarily affects the right ventricle, and it may also involve the left ventricle [33]. The presentation of disease is highly variable. COVID-19 may trigger malignant ventricular arrhythmias and unmask a clinically silent cardiomyopathy. In the study of Mukhopadhyay et al. the authors showed a case of a 57-year-old man admitted to hospital with ventricular tachycardia (VT) [33]. Patient had a history of two VT episodes requiring direct current cardioversion in the last 3 h followed by another episode in the emergency department that was cardioverted. There was no past history of cardiac illness. Systemic inflammatory markers and cardiac troponin T were progressively increased over the next 4 weeks paralleled by an increase in ventricular premature contraction burden and thereafter started decreasing and returned to baseline by sixth week when the patient became COVID-19 negative by PCR. Subsequently, a single-chamber automated implantable cardioverter-defibrillator implantation was done following which there was a transient increase in these biomarkers that subsided spontaneously. The patient was asymptomatic during 6 weeks of follow-up. The case highlights a life-threatening presentation of COVID-19 and indicates a probable link between inflammation and arrhythmogenicity.

Cardiomyopathies and COVID-19 Vaccines

There were reported some cases of stress cardiomyopathy after COVID-19 vaccines. In the study of Ho et al. there were two cases of stress cardiomyopathy associated with the Pfizer-BioNTech vaccine [34, 35]. Both patients were managed medically. On balance, the benefit of COVID-19 vaccination even in young male populations exceeds the risk of cardiac adverse events.

Considering that the outcomes of myocarditis and pericarditis post-vaccination are good, vaccine uptake in this population should be encouraged in view of the current data. In contrast to the COVID-19 vaccine, adverse reactions to other vaccines are well-known but not as widely publicized. Taken together with the risk benefit ratio of COVID-19 vaccination being highly in favor of vaccination, vaccine hesitancy to the COVID-19 vaccine needs to be addressed actively to encourage higher uptake in the general population [36, 37].

Summary

The COVID-19 pandemic has caused a large number of deaths confirmed cases worldwide, posing a serious threat to public health. Cardiovascular disease is a common comorbidity in patients with COVID-19 and such patients are at higher risk of severe disease and mortality. Acute myocardial injury, defined as an elevation in cardiac troponins, is common in hospitalized patients with COVID-19. Myocardial injury during COVID-19 can be explained by three potential mechanisms: myocardial dysfunction from the direct viral effect on cardiomyocytes—ACE2 mediated direct damage; cardiac injury indirectly due to an excessive immune inflammatory response like cytokine storm; and hypoxia, oxidative stress due to acute respiratory damage resulting in myocardial necrosis from increased myocardial oxygen demand [38].

Cardiomyopathies are one of complications of COVID-19. The most common is TTS. It may be triggered by physical causes, such as increased level of catecholamine and cytokine storm, presented during a SARS-CoV2 infection or emotional triggers related with quarantine or self-isolation. Development of TTS during COVID-19 is also connected with higher mortality rate, especially when patients develop cardiogenic shock. All high-risk patients should be consider to be treated with anticoagulants [20]. Early detection of TTS may reduce mortality and complication of cardiovascular system.

It is important to stratify holistic risk in COVID -19 patients by taking all other comorbidities such as diabetes, neurological disorders, disabilities or pulmonary diseases into consideration. It is worth to analyze the electrocardiogram and measure the levels of biomarkers, such as NT-proBNP, troponins, myoglobin, D-dimers, C-reactive protein, interleukin-2, interleukin-6, and ferritin, to evaluate the high-risk patients presenting with acute COVID-19, and help in early detection of patients in need of hospitalization.

Different pharmacological and non-pharmacological treatments have been studied and applied for COVID-19. The most common non-pharmacological management were nasal oxygen and intubation. Corticosteroids, hydroxychloroquine, azithromycin, antiviral drugs, and β-Blockers were the most common pharmacological treatments. Due to the wide range of disease symptoms and complications, further studies related to each organ involvement are required to cure the disease better and prevent the complications [39].

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