CHAPTER 41

Cardiovascular Disease in the COVID-19 Era: Myocardial Injury and Thrombosis

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KEY POINTS

- Acute cardiac injury occurs in approximately up to one-third of patients with Coronavirus disease-2019 (COVID-19), and it is associated with worse prognosis and higher mortality in these patients.
- Signs and symptoms of acute cardiac injury in COVID-19 might be nonspecific; however, laboratory tests show elevated cardiac troponin and natriuretic peptides. The ECG, chest X-ray, and echocardiography may help the physicians in detecting other cardiovascular problems, and/or complications of acute cardiac injury in COVID-19 patients.
- Acute myocardial injury may result in arrhythmias, heart failure, and cardiogenic shock.
- The COVID-19-associated coagulopathy is characterized by markedly elevated D-dimer concentration, a normal or relatively modest decrease in platelet count, and a prolongation of the prothrombin time.
- This hypercoagulable state along with prolonged bed rest and endothelial cell injury (endotheliitis) might increase the risk of thrombotic events (including pulmonary embolism) in patients with COVID-19.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; first referred to as 2019-nCoV) emerged in Wuhan, China in late December 2019, and resulted in the Coronavirus disease-2019 (COVID-19) pandemic.[1,2]

Although the primary organ involved in COVID-19 appears to be the lungs, cardiac involvement can also occur. Acute myocardial injury has been linked to worse prognosis and higher mortality in patients with COVID-19.[3–7]

The definition of acute myocardial injury is nonspecific and differed in various studies. In most studies, acute cardiac injury was defined as cardiac troponin value above the 99th percentile upper reference limit (URL) or the occurrence of new abnormalities in electrocardiography and echocardiography.[4,8] The frequency of myocardial injury has been reported to range from 7% to 28% among hospitalized patients with COVID-19.[3,5,8–10] However, data on the frequency of myocardial damage in outpatient setting is lacking.

According to the Fourth Universal Definition of Myocardial Infarction (2018), the 99th percentile URL is considered as the decision level for the diagnosis of myocardial injury[11]; however, this cutoff level includes all conditions causing "myocardial cell death" with subsequent elevation in cardiac troponin levels. Based on the data from case series and reports, putative causes of myocardial injury include:

- **Ischemic causes:**
  - Acute coronary syndrome caused by either plaque instability and rupture (type I myocardial infarction) or demand ischemia (type II myocardial infarction)
  - Endotheliitis[12] leading to endothelial dysfunction and microvascular damage
- **Nonischemic causes:**
  - Hypoxic injury
  - Stress cardiomyopathy (i.e., takotsubo cardiomyopathy)[13,14]
  - Profound systemic inflammatory response/cytokine storm leading to myocardial suppression
  - Right heart failure[15–17] (i.e., acute cor pulmonale), may result from pulmonary thromboembolism, pulmonary hypertension caused by ARDS (due to hypoxemic vasoconstriction, vascular remodeling, external compression of the vasculature by edema or fibrosis, and reduced pulmonary compliance), and high-pressure mechanical ventilation

SARS-CoV-2 uses transmembrane ACE2 receptors to enter the host cells. In addition to type-2 pneumocytes, the ACE2 receptors are expressed on cardiac myocytes, endothelial cells, and pericytes.[18,19] This might also contribute to the cardiac damage in SARS-CoV-2 infection, though the exact pathophysiologic mechanisms are still unclear.

Key cardiovascular manifestation of COVID-19 and suggested pathophysiologic mechanisms are summarized in Fig. 41.1.[20]

Key Points

- Although the clinical presentation of myocarditis has been described in a few case reports in patients with COVID-19,[21,22] viral myocarditis caused by direct invasion of SARS-CoV-2 to myocardial tissue has not been definitively confirmed by histologic examinations and viral genome assays.
- Despite considerable incidence and prognostic implications of acute cardiac injury in hospitalized patients with COVID-19, there is insufficient evidence to recommend routine measurement of cardiac troponin to screen for acute myocardial injury in all COVID-19 patients.
- However, patients with history of prior coronary artery disease (CAD), structural heart disease, diabetes mellitus, hypertension, and chronic kidney disease tend to have more severe COVID-19 infection; and should be closely monitored for the occurrence of acute myocardial injury.

DIAGNOSTIC APPROACH TO PATIENTS WITH ACUTE CARDIAC INJURY

Cardiac injury symptoms are nonspecific in COVID-19 and patients mostly present with the typical symptoms of SARS-CoV-2 infection, including fever, cough, dyspnea, or fatigue and a minority present with anginal chest pain and palpitations. A new-onset and/or unexplained dyspnea, orthopnea, peripheral edema, and jugular venous distension should raise clinical suspicious for cardiac involvement in patients with severe COVID-19 infection.

In clinically suspected patients, the diagnostic approach should include the following.

Electrocardiogram

- A 12-lead electrocardiogram (ECG) should be obtained initially in all patients with suspected myocardial damage. The most common ECG abnormality reported in patients with acute cardiac injury was ST-segment elevation or depression, T-wave depression and inversion, and Q waves. The QT interval (and corrected QT interval) should also be assessed, in particular in patients on QT-prolonging therapies.
- Initial ECG may provide clues to specific diagnoses, which require a change in management.
  - QT prolongation of >500 ms or ventricular tachycardia in patients receiving certain medications (including chloroquine, hydroxychloroquine, lopinavir–ritonavir, azithromycin, etc.) may result in early discontinuation and replacement of the responsible medication.
  - New pathologic Q waves, ST-T changes, or arrhythmia would mandate further cardiac assessments such as echocardiography.
- Various tachy- or bradyarrhythmia would require close electrolyte assessments, QT measurement, inotrope/vasopressor change, or proper therapies (antiarrhythmics/cardioversion).

Routine Laboratory Tests

- A complete blood count (with differential), blood glucose, blood urea nitrogen, creatinine, serum electrolytes, and liver function tests should be assessed in all patients.

Chest X-ray

- Although bilateral chest infiltration from the underlying pneumonia and ARDS from COVID-19 infection may obscure abnormalities caused by cardiac dysfunction, a CXR may help in the detection of cardiomegaly and pleural effusions.

Cardiac Troponins

- A cardiac troponin value above the 99th percentile upper reference limit is indicative of acute myocardial injury.[11] Since an elevated troponin level in patients with COVID-19 is nonspecific and multifactorial, the results should be interpreted based on the clinical presentation, ECG findings, and echocardiographic examination.

Natriuretic Peptides (BNP or NT-proBNP)

- Natriuretic peptides are mainly released from the heart in response to increased myocardial wall stress. Several studies have demonstrated elevated BNP or NT-proBNP levels in COVID-19 patients, and an elevated NT-proBNP level has been associated with worse outcomes in patients with severe COVID-19.[23,24] However, it should be noted that elevated NT-proBNP level has been reported in patients with acute lung injury and acute respiratory distress syndrome from other causes,[25–30] even in the absence of clinical findings of heart failure; therefore, an elevated NT-proBNP level should be interpreted based on the whole clinical presentation.

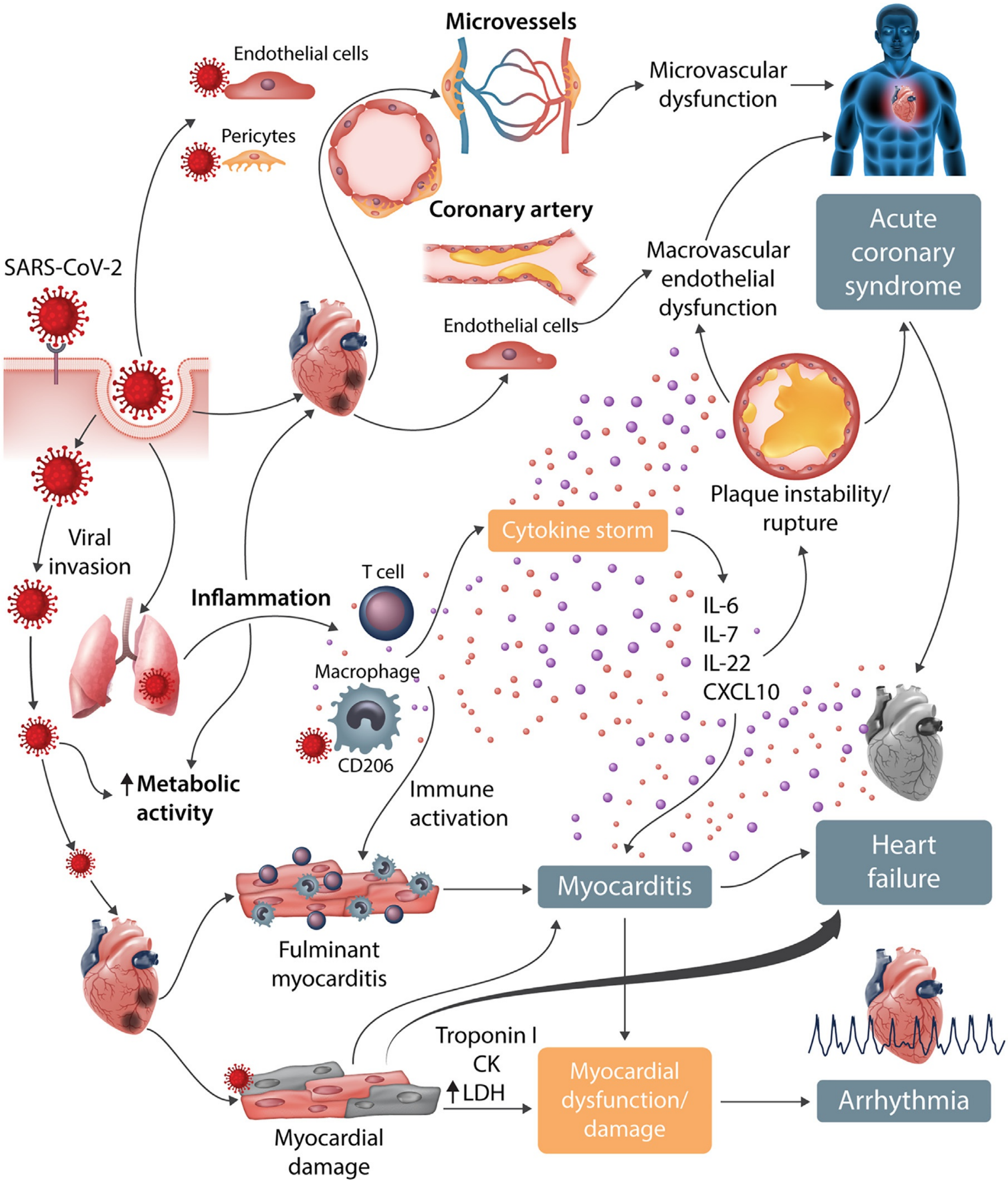

FIG. 41.1 For figure Legend see next page

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FIG. 41.1, CONT'D Cardiovascular involvement in COVID-19—key manifestations and hypothetical mechanisms. SARS-CoV-2 anchors on transmembrane ACE2 to enter the host cells including type 2 pneumocytes, macrophages, endothelial cells, pericytes, and cardiac myocytes, leading to inflammation and multiorgan failure. In particular, the infection of endothelial cells or pericytes could lead to severe microvascular and macrovascular dysfunction. Furthermore, in conjunction with the immune over-reactivity, it can potentially destabilize atherosclerotic plaques and explain the development of the acute coronary syndromes. Infection of the respiratory tract, particularly of type 2 pneumocytes, by SARS-CoV-2 is manifested by the progression of systemic inflammation and immune cell overactivation, leading to a "cytokine storm," which results in an elevated level of cytokines such as IL-6, IL-7, IL-22, and CXCL10. Subsequently, it is possible that activated T cells and macrophages may infiltrate infected myocardium, resulting in the development of fulminant myocarditis and severe cardiac damage. This process could be further intensified by the cytokine storm. Similarly, the viral invasion could cause cardiac myocyte damage directly leading to myocardial dysfunction and contribute to the development of arrhythmia. (From Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116(10):1666–1687; with permission.)

Echocardiography

- Currently, there is insufficient evidence to recommend routine echocardiography for all COVID-19 patients with suspected cardiac damage. Considering the limitations in personal protective equipment and the importance of social distancing, the echocardiographic examination can be tailored to the presentation of each individual patient.
- In selected cases, point-of-care ultrasonography (POCUS) and focused cardiac ultrasound study (FoCUS) could help in detecting gross abnormalities in cardiac structure and/or function. These bedside options may also be performed by the trained non-cardiologists who might already be in the room with these patients, thereby reducing the risk of cardiologists' exposure to the virus.

COMPLICATIONS OF CARDIAC INJURY IN COVID-19

Arrhythmias and Conduction Abnormalities

Although no specific arrhythmia has been linked to SARS-CoV-2 infection, both brady- and tachyarrhythmias, as well as sudden cardiac death have been reported in patients with COVID-19.[5,6,31–33]

Myocardial injury and damage to the conduction system, as well as hypoxia may be directly related to the development of arrhythmias in these patients. Arrhythmias can also occur as a complication of electrolyte abnormalities, acute heart failure, acute coronary syndrome, myocarditis, and cardiogenic and/or septic shock in patients with COVID-19.

In addition, QT-prolongation has been reported in COVID-19 patients, even though the majority of cases seemed to be drug-induced, mostly related to chloroquine, hydroxychloroquine, and azithromycin.[34–36]

Epidemiologic studies also reported an increased incidence of out-of-hospital cardiac arrest during COVID-19 pandemic[37,38]; however, other factors such as increased stress during the pandemic, and unwillingness or delay in seeking medical care by patients with cardiac problems might also be responsible in addition to COVID-19 infection.

Heart Failure

In patients with COVID-19, both de novo acute heart failure and acute decompensation of chronic heart failure might develop.

- In addition to heart failure with reduced ejection fraction (HFrEF), the occurrence of heart failure with preserved ejection fraction (HFpEF) should also be considered in COVID-19 patients failure.[39] Acute myocardial injury, cytokine-induced inflammatory state, comorbidities such as hypertension, side effects of medications, and vigorous intravenous fluid administration might impair myocardial relaxation, in particular in the elderly and those with underlying diastolic dysfunction, resulting in acute heart failure.
- The presence of potential precipitating factors for acute decompensation of chronic heart failure should be carefully assessed and monitored in COVID-19 patients.
- Patients with previous history of chronic heart are recommended to continue their previous guideline-directed medical therapy, including

beta-blockers, ACE inhibitors or angiotensin II receptor blockers, and mineralocorticoid receptor antagonists.[40]
- When administering intravenous fluids to these patients, attempt should be done to avoid both volume overload and circulatory failure.
- For the management of fever, nonsteroidal antiinflammatory drugs (NSAIDs) should be used with caution in these patients, considering their potential effect on water and sodium retention; thus, acetaminophen may be generally preferred in these patients.

Cardiogenic Shock

In patients with COVID-19, cardiogenic shock may be caused by:
- Acute decompensated heart failure
- Myocardial infarction
- Myocarditis
- Sustained refractory arrhythmia

In critically ill patients with COVID-19, a combination of cardiogenic shock and septic shock (mixed shock) may contribute to hemodynamic deterioration and impaired end-organ perfusion.

THROMBOSIS IN THE COVID-19 OUTBREAK

Since the early report from China, an unusual increased coagulopathy has been reported in COVID-19 population.[7] In several population-based studies, non-survived population had significantly higher levels of D-dimer and fibrin degradation products and longer prothrombin and activated partial thromboplastin times (aPTT), which also confirmed an important prognostic role for the coagulopathy.[41] Initially, the nature of this coagulopathy was related to the accompanied septic shock and disseminated intravascular coagulation (DIC).[7] In one of the early reports, Tang et al. observed that DIC occurred in 71.4% of the non-survivors vs 0.6% of the survivors during hospitalization.[41] However, as our knowledge grew, it became more apparent that a direct viral impact on the coagulation cascade may also play a role. For instance, in a report by Klok et al., none of the ICU patients with thrombotic complication developed DIC.[42]

Venous Thromboembolism

The described coagulopathy, along with prolonged bed rest and concomitant therapeutic regimen, increase the risk of thrombotic events in COVID-19.[43] Depending on the screening methods, investigation sites (wards vs ICUs) and the use of thrombophylaxis, incidence of thrombotic events varies across studies between 7% and 85%.[31,42,44–49] Klok et al. observed a 31% (95% CI: 20%–41%) incidence of thrombotic complications in three academic/teaching hospitals in the Netherlands, the majority of which were venous thromboembolism (VTE).[42] High incidence (20.6%) of pulmonary embolism has also been reported by Poissy et al. at least two times higher than previous year during the same time interval.[44] In a report by Middeldorp et al., the incidence of VTE in ICU was significantly higher than ward [59% (95% CI: 42–72) vs 9.2% (95% CI: 2.6–21)].[46] In addition, several postmortem studies have frequently shown the presence of pulmonary micro- and macrothrombosis and deep vein thrombosis, at times as the cause of unexpected death.[50,51]

It should be noted that diagnosis of VTE might be very challenging in patients hospitalized for COVID-19: the inapplicability of D-dimer, issues with transferring to imaging wards, and difficulties in optimal patient positioning have left the diagnostic process of considerable numbers of patients, particularly the sickest, incomplete.[52] Although not definite, but some diagnostic measures like right ventricular enlargement/dysfunction in echocardiography or deep venous thrombosis in lower limb detected by ultrasound might be helpful toward the diagnosis of pulmonary embolism.[52] There is a clear controversy on the treatment of patients without definite diagnosis (i.e., incomplete diagnosis), and intermediate to full-dose anticoagulation have been suggested by some experts.[52]

The symptom overlap between pulmonary emboli and acute respiratory disease in COVID-19[53] and the mentioned challenges in diagnosis and treatment of pulmonary embolism call for an appropriate prophylaxis strategy. Tang et al. investigated the validity of the sepsis-induced coagulopathy score and the D-dimer level in the risk stratification of patients with COVID-19 with regard to VTE prophylaxis.[54] In their retrospective analysis on 449 hospitalized COVID-19 patients, no 28-day mortality benefit was observed among heparin (LMWH or UFH) users vs nonusers. However, in patients with a minimum sepsis-induced coagulopathy score of 4 or a D-dimer level of greater than 3.0 μg/mL, heparin prophylaxis significantly improved the 28-day mortality. Hence, Tang and colleagues recommended prophylaxis application based on risk stratification.[54] Other risk stratification tools (e.g., Caprini and IMPROVE) have also been suggested to be applied.[52] The International Society on Thrombosis and Haemostasis (ISTH) has offered a liberal recommendation suggesting the administration of LMWH in all patients hospitalized for COVID-19 (including those that are not critically ill) who do not have contraindications (platelet count ≤25,000/L or active bleeding).[55] This routine approach might be justified by the high incidence of VTE (27%) observed in hospitalized COVID-19 patients. Of note, mechanical prophylaxis has been suggested for patients with contraindication for pharmacological prophylaxis.[52]

Although the importance of VTE prophylaxis has been recognized since the early days of pandemic, it still seems to be overlooked. Wang et al. in their short report showed that more than 40% of the 1026 hospitalized patients with COVID-19 had a Padua Prediction Score ≥4 (i.e., high risk for[41] VTE), yet only 7% received appropriate treatment.[41]

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