

Cardiovascular Implications of COVID-19 Infections

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ABSTRACT: Since early 2020, the world has been facing a pandemic caused by the novel coronavirus SARS-CoV-2. Although this positive single-stranded RNA virus primarily causes pulmonary infection and failure, it has been associated with multiple cardiovascular diseases including troponin elevation, myocarditis, and cardiac arrhythmias. Cardiac patients are susceptible to developing more severe infection from SARS-CoV-2, making management complicated. In this review we discuss the cardiac manifestations of COVID-19 infections as well as considerations for the management of primary cardiac pathologies during this pandemic.

BACKGROUND

In December 2019, an outbreak of pneumonia cases was reported in Wuhan, China, caused by a newly identified β -coronavirus, now called SARS-CoV-2. SARS-CoV-2 is a positive single-stranded RNA virus believed to have originated from bats (based on genomic similarities) and transmitted to humans through unidentified intermediate hosts.¹ Human-to-human transmission is believed to occur via respiratory droplets; however, aerosol transmission is also possible. Experiments by van Doremalen et al. studied the viability of the virus in aerosols and on plastic, stainless steel, copper, and cardboard. They found that the virus remained viable in aerosols for at least 3 hours, the duration of the experiment. No viable SARS-CoV-2 was detected after 4 hours on copper or 24 hours on cardboard. It was more stable on plastic and stainless steel, with viable virus being detected up to 72 hours after application.² Due to the stability and relatively higher reproduction number of this virus, coronavirus disease-19 (or COVID-19) has, over a very short period of time, escalated to pandemic status (as declared by the World Health Organization on March 11, 2020) and is responsible for the ongoing wave of mortality across the world.

COVID-19 patients commonly present with minor respiratory symptoms such as cough, fatigue, fever, and sputum production. A minority progress to develop severe respiratory symptoms and respiratory failure. Guan et al. reported that the most common patterns on chest computed tomography (CT) were ground-glass opacities and bilateral patchy shadowing (Figure 1).³ As the scientific community learns more about COVID-19, it is emerging that this is not just a disease of the respiratory system; rather, its severe form is associated with a systemic inflammatory process that impacts the entire cardiovascular system.^{4,5} In this paper, we review the cardiovascular implications of COVID-19 (Figure 2). We discuss the increase

in COVID-19–related mortality in patients with cardiovascular diseases (CVD), the cardiovascular presentations and complications of COVID-19 along with suggested management strategies, cardiovascular considerations for the use of COVID-19 therapeutics, and implications for patients who are heart transplant recipients and those with advanced heart failure (HF).

HOW CAN COVID-19 AFFECT THE CARDIOVASCULAR SYSTEM?

The renin-angiotensin system is believed to play a central role in the pathogenesis of COVID-19. Normally, this pathway is

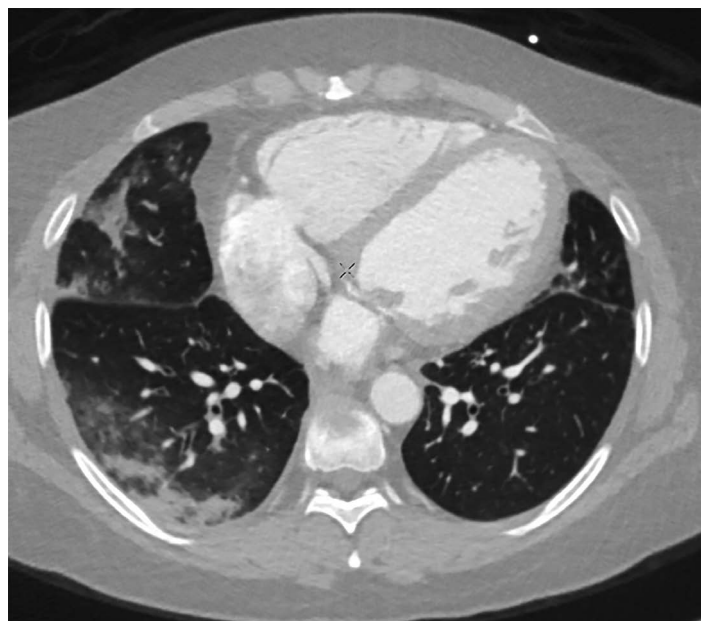


Figure 1. Representative chest computed tomography of a patient who was admitted with COVID-19.

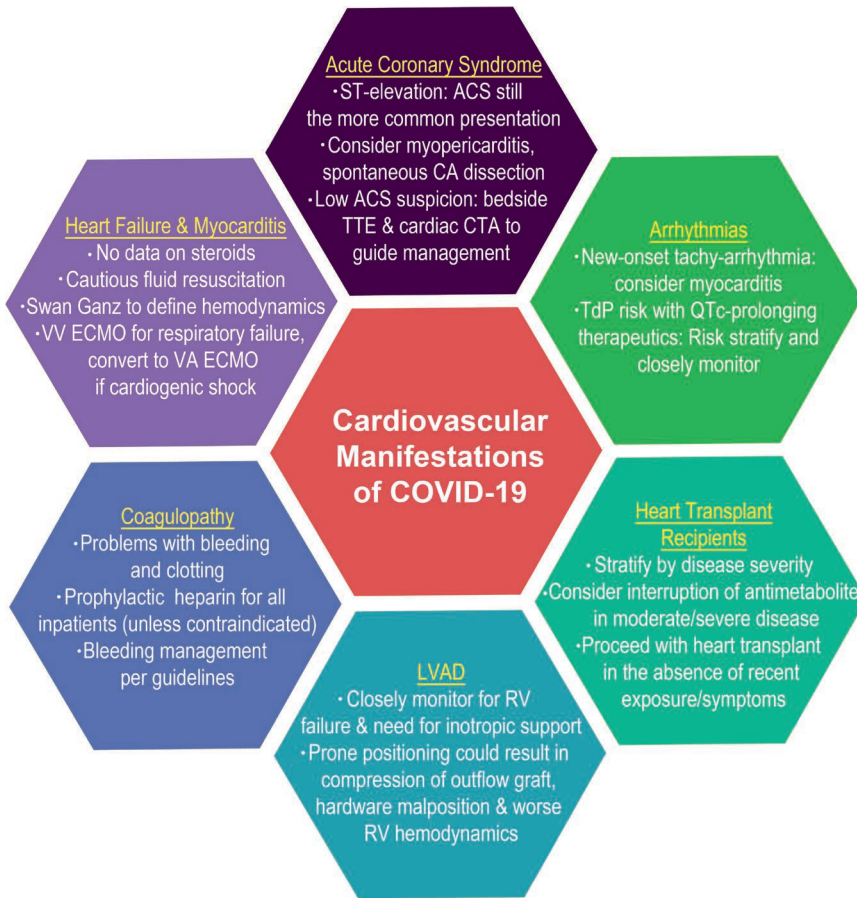


Figure 2.

Schematic representing the cardiovascular manifestations of COVID-19. CA: coronary artery; VV ECMO: veno-venous extracorporeal membrane oxygenation; VA ECMO: veno-arterial ECMO; ACS: acute coronary syndrome; TTE: transesophageal echocardiogram; CTA: computed tomography angiography; TdP: Torsades de Pointes; RV: right ventricular

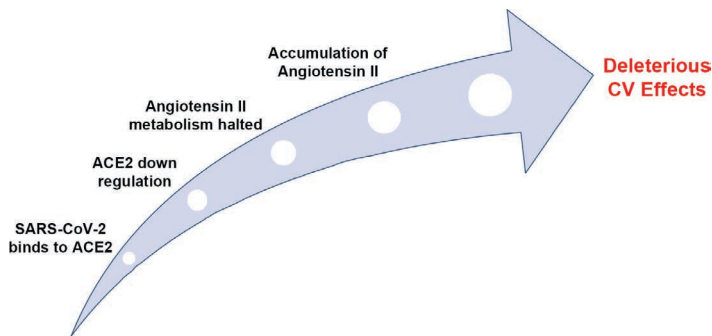


Figure 3.

Proposed mechanism of cardiovascular (CV) damage by SARS-CoV-2. ACE2: angiotensin-converting enzyme 2

triggered by a decrease in renal blood flow that stimulates the secretion of renin, which converts angiotensinogen to angiotensin I (ATI). Further, angiotensin converting enzyme (ACE) converts ATI to angiotensin II (ATII), which mediates deleterious effects such as increases in sympathetic activity, vasoconstriction, aldosterone secretion (causing renal sodium and water reabsorption), pulmonary vascular permeability, and fibrosis. In the presence of the ACE2 protein (found on endothelial cells, arterial smooth muscle, immune cells, and respiratory and small bowel epithelia), ATII is converted to angiotensin, which counteracts its effects.⁶

The ACE2 protein also serves as a receptor and point of cellular entry for SARS-coronaviruses. Binding of the SARS-CoV-2 spike protein to the ACE2 protein is followed by endocytosis of the virus and subsequent viral replication as well as ACE2 downregulation. Lack of ACE2 may decrease the conversion of ATII to angiotensin, leading to an accumulation of ATII and increase in its deleterious effects, including those on the cardiovascular system (Figure 3).⁷

Another possible mechanism for cardiovascular morbidity in patients with COVID-19 is related to the systemic inflammatory response, which may trigger atherosclerotic plaque rupture, myocarditis, and arrhythmias.⁵

THE DILEMMA OVER ACE INHIBITOR AND ANGIOTENSIN RECEPTOR BLOCKER USE DURING COVID-19

A significant number of patients with CVD such as HF and hypertension are on ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). These medications have been shown to cause upregulation of ACE2 receptors in animal models.^{8,9} As previously explained, SARS-CoV-2 binds to ACE2 for cell entry; therefore, it is conceivable that the upregulation of ACE2 by ACEIs/ARBs

may increase the virulence of SARS-CoV-2. However, to date, this has not been proved clinically.

On the other hand, the use of renin-angiotensin blockers may be beneficial to patients with COVID-19 given that unopposed ATII action is believed to be involved in the disease pathogenesis.⁷ To this end, upcoming clinical trials will assess whether use of the ARB losartan may have beneficial effects in inpatients and outpatients with COVID-19 in the United States.¹⁰

In the absence of randomized controlled trials to study this phenomenon, Zheng et al. recently analyzed clinical data from 1128 patients with hypertension who were diagnosed with COVID-19. Of these, 188 were on ACEIs or ARBs, and the authors observed a lower rate of mortality in this group. This difference remained consistent in unadjusted analysis and after adjusting for imbalanced variables in a propensity score matched analysis.¹¹ Given the current absence of strong evidence for harm from the use of ACEIs/ARBs in COVID-19, it is recommended that patients remain compliant with these medications. Adding ACEIs/ARBs specifically for the treatment of COVID-19 is currently not recommended.^{9,12}

INCREASED COVID-19 MORTALITY IN PATIENTS WITH CVD AND CVD RISK FACTORS

While the overall case fatality rate for COVID-19 was reported to range between 1.4% and 2.3% in China,^{3,13} the rates of mortality are much higher for patients elsewhere and in patients with CVD or CVD risk factors—10.5% in patients with CVD, 7.3% in those with hypertension, and 6% in those with diabetes mellitus.¹⁴ The cause for the significant increase in mortality in this population may be multifactorial and perhaps similar to the association between influenza and CV events.^{15,16} Mechanisms for increased mortality may include vulnerable plaque rupture, increase in myocardial demand, HF and myocarditis, arrhythmias, and baseline frailty in a subset of patients.^{15,16}

A retrospective study by Shi et al. analyzed the outcomes of 416 patients hospitalized with COVID-19 in China and found that high-sensitivity troponin I was elevated in 19.7% of patients and was associated with increased mortality in a multivariate analysis.¹⁷ Similarly, a retrospective study by Guo et al. showed that in a cohort of 187 patients with COVID-19, elevated troponin T was present in 27.8%. Of these, 59.6% died compared to 8.9% in the group without elevated troponin.¹⁸ However, limitations of these studies included their retrospective nature and not accounting for the time of troponin measurement.

Common causes for troponin elevation in COVID-19 patients include acute coronary syndrome, demand ischemia, myocarditis, arrhythmias, and microangiopathy (Figure 4).

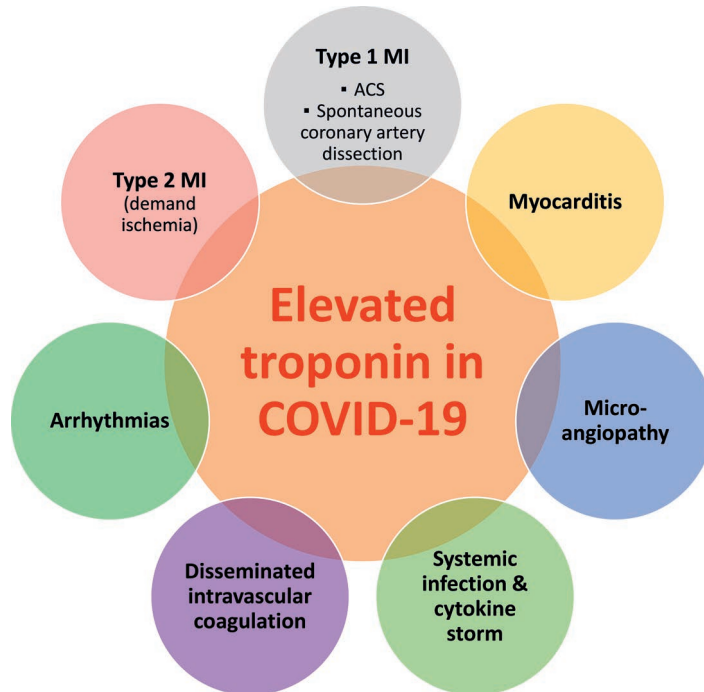


Figure 4.

Common causes for elevated troponin level in patients with COVID-19. MI: myocardial infarction; ACS: acute coronary syndrome

The American College of Cardiology currently recommends measuring troponin levels in COVID-19 patients only when considering the diagnosis of acute coronary syndrome on clinical grounds¹⁹; however, based on the above data, it appears that troponin levels may be a useful triaging tool and prognostic marker in patients hospitalized with COVID-19. Given the lack of strong evidence at this time, the decision to use troponin as a triaging/prognostic marker must be balanced against the risk of triggering excessive downstream testing after an elevated troponin is reported.

ACUTE CORONARY SYNDROMES IN COVID-19

The true incidence of acute coronary syndrome (ACS) in patients with COVID-19 is not known; however, there appears to be a remarkable decrease in the overall hospital presentations for ACS worldwide.²⁰ The reasons for this are speculative. It is theoretically possible for COVID-19 patients to have concomitant ACS, and management in these cases may require complex decision making. Considerations revolve around balancing appropriate patient care with ensuring the safety of healthcare workers and limiting the number of people exposed to SARS-CoV-2. It is important for healthcare providers to familiarize themselves with the guidance provided by cardiovascular societies such as the Society for Cardiovascular

Angiography and Interventions as well as with local institutional protocols.

Broadly, in patients presenting with ST-elevation myocardial infarctions (STEMI) with high-risk features such as anterior infarct location, hypotension, HF, cardiogenic shock, and life-threatening arrhythmias, primary percutaneous coronary interventions should be considered as first-line treatment. Other STEMI patients who are hemodynamically and clinically stable may receive fibrinolytic therapy or be managed conservatively.²¹ Similarly, patients with non-STEMIs should also be stratified by risk, with high-risk patients triaged to early angiography and low-risk patients managed conservatively.²¹

For patients with respiratory distress, a lower threshold for intubation may be prudent to decrease the risk of aerosolizing in the catheterization laboratory. Furthermore, some procedures may be done at bedside instead of the catheterization laboratory, such as intra-aortic balloon pump placement or pulmonary arterial catheterization.²²

HEART FAILURE, MYOCARDITIS, AND COVID-19

Although patients with underlying HF may be more susceptible to developing COVID-19, it appears that patients with COVID-19 may also develop new-onset HF. Arentz et al. published a case series comprising 21 patients in Washington state and found that 42.9% of these patients had comorbid HF at the time of presentation and 33% appeared to have developed cardiomyopathy in the setting of COVID-19.²³ Inciardi et al. published a case report showing CMR evidence of acute myocarditis in a COVID-19 patient who presented with new-onset HF and inferior and lateral ST elevations on electrocardiogram (EKG).²⁴ Similarly, there have been anecdotal reports on online forums of patients presenting with ST elevations on EKG suggestive of STEMI but found to have patent coronary arteries and evidence of new-onset HF. It is not yet clear whether a majority of these cases of new-onset HF occur due to direct viral invasion, myocardial inflammation, or as a form of reversible stress-induced cardiomyopathy. Xu et al. examined myocardial specimens during an autopsy on a patient who died from COVID-19 and found evidence of interstitial mononuclear inflammatory infiltrates in the myocardium.²⁵

Regardless of the pathophysiology of HF in these patients, it appears that the presence of comorbid HF may portend a worse prognosis. Ruan et al. analyzed the cause of death in 68 fatal cases of COVID-19 and found that HF was implicated either by itself or with respiratory failure in 40% of the cases.²⁶

Given these data, it is essential to closely monitor these patients and aggressively treat HF. Hu et al. reported a case of a 37-year-

old male with fulminant myocarditis in the setting of COVID-19 treated with methylprednisolone 200 mg/day for 4 days and intravenous immune globulin therapy 20 g/day for 4 days; he had echocardiographic recovery of cardiac size and function in one week. In this case, however, the diagnosis of myocarditis was based primarily on echocardiography and hemodynamics and true inflammation of the myocardium was not confirmed.²⁷

In the absence of strong data supporting the use of steroids or other immunomodulatory agents in patients with new-onset HF in the setting of COVID-19, we recommend managing these patients supportively with guideline-directed medical therapy for HF with reduced ejection fraction, afterload reduction, and in cases of cardiogenic shock, with inotropes (which may require mechanical circulatory support). Exceptions to this may include patients who are part of a clinical trial or if benefits of immunomodulation outweigh the risks as determined by an expert opinion from an HF cardiologist. Other considerations include exercising caution with volume resuscitation in patients who may have presented with sepsis, considering the diagnosis of right-sided HF in the setting of acute respiratory distress syndrome and elevated pulmonary pressures, and defining hemodynamics using pulmonary arterial catheterization when there is a concern for cardiogenic shock, especially while considering the role for extracorporeal membrane oxygenation.²⁸

ARRHYTHMIAS IN COVID-19

Patients with COVID-19 appear to have an increased incidence of arrhythmias, likely in the setting of metabolic abnormalities, hypoxemia, and acidosis.²⁸ Wang et al. reported a series of 138 patients in which the incidence of arrhythmias was 16.7%.²⁹ Another publication by Guo et al. reported that in a cohort of 187 patients, the incidence of ventricular tachycardia or fibrillation was 5.9%.¹⁸ In such patients who present with a malignant tachyarrhythmia and elevated troponin, it is important to consider evaluation for myocarditis.²⁸

Further, agents used for COVID-19 treatment may have arrhythmogenic potential due to QTc prolongation. Of special concern is the use of hydroxychloroquine and azithromycin for prevention and treatment of COVID-19 (neither drug is currently approved for COVID-19 indications by the US Food and Drug Administration). At present, given the lack of strong scientific evidence of benefit of these agents, the American College of Cardiology recommends that they only be used in the setting of a clinical trial or at the direction of an infectious disease or COVID-19 expert, with cardiology input regarding QT monitoring.³⁰ Patients can be risk stratified using the Tisdale score to identify those at a higher risk for developing drug-induced QT prolongation (Table 1).^{30,31} In patients receiving hydroxychloroquine and/or azithromycin, a baseline EKG must

RISK FACTORS	POINTS
Age ≥ 68 years	1
Female sex	1
Loop diuretic	1
Serum K ⁺ ≤ 3.5 mEq/L	2
Admission QTc ≥ 450 ms	2
Acute MI	2
≥ 2 QTc-prolonging drugs	3
Sepsis	3
Heart failure	3
One QTc-prolonging drug	3
Maximum risk score	21
Low risk: ≤ 6 pts; moderate risk: 7-10 pts, high risk: ≥ 11 pts	

Table 1.
The Tisdale score can be used to identify patients at high risk for developing drug induced QTc prolongation.³¹ K⁺: potassium; MI: myocardial infarction

be obtained along with renal and hepatic function, serum potassium, and magnesium. All nonessential QT-prolonging medications must be discontinued. It is recommended that a repeat EKG be performed 2 to 3 hours after dosing on day 3 of therapy. Indications for discontinuation would be if QTc increases by > 30 to 60 msec or absolute QTc increased to > 500 msec (or > 530-550 msec if QRS > 120 msec).³⁰

While a 12-lead EKG remains the conventional method to measure QTc, this may be difficult in some inpatients who are COVID-19 positive where it may be prudent to limit exposure of personnel, or in patients who are in a prone position as part of acute respiratory distress syndrome treatment. In these cases, QTc may be obtained from continuous telemetry using electronic calipers. Obtaining a 12-lead EKG may also be challenging in outpatients on hydroxychloroquine and/or azithromycin. Hand-held devices may present an alternative in this situation. A recent study by Cheung et al. evaluated 22 patients undergoing routine evaluation for an inherited

arrhythmia syndrome using the AliveCor Kardia hand-held EKG monitoring device (AliveCor, Inc.). Sequential single-lead EKGs in leads I, II, and precordial positions were obtained using the handheld device. There was no difference in the maximal QTc interval measured by 12-lead EKG compared to the maximal QTc interval measured across all positions using the handheld device (401 vs 404 ms, $P = .259$).³² These results are promising, and it is likely that using such hand-held devices may benefit patients not only in the COVID-19 era but also in years to come.

COAGULOPATHY IN COVID-19 INFECTIONS

Severe COVID-19 infection is frequently complicated by coagulopathy and disseminated intravascular coagulation (DIC).³³⁻³⁵ This likely represents a culmination of several mechanisms: sepsis, systemic inflammation, and cytokine storm are well recognized as causes for DIC where there may be a dysfunction of endothelial cells resulting in excess thrombin generation and fibrinolysis stimulation systemically and locally in the lungs.³⁵ In addition, these critically ill patients are predisposed to develop deep venous thrombosis (DVT) and embolism. Cui et al. reported the incidence of lower-extremity DVT in patients with severe COVID-19 pneumonia to be 25% (20 of 81 patients).³⁶

While there is no specific treatment for the coagulopathy associated with COVID-19 infections, the International Society on Thrombosis and Hemostasis recommends standard thromboprophylaxis for all admitted patients without contraindications (such as active bleeding and platelet count < $25 \times 10^9/L$).³⁷

Tang et al. reported data from 449 patients with severe COVID-19 infection, of whom 99 received heparin for at least 7 days (94 received 40-60 mg/day low-molecular-weight heparin and 5 received 10,000-15,000 U/day of unfractionated heparin). The group that received heparin had lower 28-day mortality and a sepsis-induced coagulopathy score of ≥ 4 or D-dimer > 6 times the upper limit of normal.³⁸ It is postulated that the use of prophylactic heparin is beneficial not only to prevent DVTs but also to exert an anti-inflammatory effect.³⁷ Finally, patients with bleeding issues should be treated per usual septic coagulopathy guidelines.³⁷

CONSIDERATIONS FOR HEART TRANSPLANT RECIPIENTS AND PATIENTS WITH ADVANCED HEART FAILURE

A recent survey of 87 heart transplant recipients in China showed that 96.6% of them undertook adequate precautions against getting infected by SARS-CoV-2; in this group, there were no documented cases of COVID-19 over 2 months of

follow-up.³⁹ The International Society for Heart and Lung Transplantation (ISHLT) recommends that heart transplant recipients, patients with advanced HF, and pulmonary hypertension patients who present with COVID-19 should be managed depending on disease severity: Patients with mild disease should be quarantined at home with frequent telephone follow-up, and those with moderate and severe severity should be managed as inpatients.⁴⁰

Given the above, the ISHLT recommends that organ harvesting and transplantation continue during the COVID-19 pandemic provided that neither the donor nor the recipient have active or recent COVID-19 infection. Donors must be tested for COVID-19 prior to harvest, and testing must also be considered for recipients.⁴⁰

CARDIOVASCULAR IMAGING SERVICES DURING THE COVID-19 PANDEMIC

Although patient safety is an important consideration during the COVID-19 pandemic, it is also imperative to consider the risk of exposing staff during elective procedures and imaging tests. To limit the spread of COVID-19, the general consensus is to restrict procedures and investigations to only emergency cases where the procedure or investigation is likely to change management or patient outcomes. To this effect, all the major cardiovascular societies have released recommendations regarding the use of diagnostic investigations during the COVID-19 pandemic, summarized as follows.

Echocardiography

The portability of echocardiography offers an advantage over other imaging modalities in that it can be done at bedside and requires only one technician to perform the study. The American Society of Echocardiography recommends using the appropriate use criteria (AUC) to determine which patients require an echocardiogram. Appropriate studies that are urgent or emergent should be performed and all others deferred as long as this does not pose any significant risk to patients. The study should be performed at a location that minimizes the risk of virus transmission in the clinic or hospital. Based on the indication of the study, echocardiographic examinations should be planned to obtain limited, focused views to answer the question at hand. All efforts should be made to minimize scan times, and appropriate personal protective equipment must be used while scanning.

There is a heightened risk of spreading SARS-CoV-2 during transesophageal echocardiography (TEE) due to the risk of aerosolization of virus particles when the patient coughs or gags during the examination. TEE should not be performed if

the question can be answered by another imaging modality. If TEE needs to be performed on a patient with suspected or confirmed COVID-19, airborne precautions must be used.

Treadmill or bicycle stress echocardiography may lead to virus transmission from the patient due to deep breathing and/or coughing during exercise; these tests should be converted to a pharmacological stress approach or deferred.⁴¹

Cardiac CT (CCT)

The use of cardiac CT (CCT) should be determined on a case-by-case basis, balancing the risk of transmission against the expected benefit. Due to the low risk of aerosolization of virus particles during CCT, this modality is preferred over TEE where appropriate (eg, evaluation for left atrial appendage or intracardiac thrombus prior to cardioversion). Some urgent indications where performing a CCT may be appropriate include structural interventions or evaluating left atrial appendage, LVAD dysfunction, acute symptomatic prosthetic valve dysfunction, endocarditis and its complications, suspected new malignant cardiac masses, or coronaries in stable patients with acute chest pain.⁴²

Nuclear Cardiology

As with other imaging modalities, nuclear imaging studies should be performed judiciously in cases where they are absolutely indicated. Laboratories should select the protocol with the shortest scan time and lowest staff exposure. This may mean using standard dose imaging with rapid imaging protocols, performing stress tests first, single-day imaging protocols, and making increased use of attenuation-corrected imaging. If available, positron emission tomography is preferable given its rapid throughput that minimizes the time that patients spend in the laboratory.⁴³

Cardiac MRI

Requests to perform cardiac MRI (CMR) should be reviewed by a CMR physician to determine appropriateness. When CMR is absolutely indicated, the study should be performed using abbreviated protocols.

CONCLUSION

The landscape of COVID-19 management is rapidly evolving and, given the extensive involvement of the cardiovascular system in this novel disease, it is clear that cardiovascular healthcare providers will continue to remain heavily involved in the care of these patients. Providers should expect more data in the upcoming months and stay updated on the latest advances.

KEY POINTS

- Emerging evidence shows that severe COVID-19 is associated with a systemic inflammatory response impacting the entire cardiovascular system. Mortality rates are much higher for patients with cardiovascular disease or its risk factors.
- Given the current absence of strong evidence for harm from the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in COVID-19, it is recommended that patients remain compliant with these medications.
- Patients with underlying heart failure (HF) may be more susceptible to developing COVID-19, and it appears that patients with COVID-19 may also develop new-onset HF.
- Some agents proposed to treat COVID-19, especially hydroxychloroquine and azithromycin, carry an increased risk for arrhythmias.
- To limit the spread of COVID-19, restrict procedures and investigations to only emergency cases where they are likely to change management or patient outcomes.

Conflict of Interest Disclosure:

The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:

COVID-19, ACE inhibitors, angiotensin receptor blockers, arrhythmias, organ transplant, coagulopathy, cardiovascular imaging, troponin

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