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A current review of COVID-19 for the cardiovascular specialist

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Abstract Although coronavirus disease 2019 (COVID-19) predominantly disrupts the respiratory system, there is accumulating experience that the disease, particularly in its more severe manifestations, also affects the cardiovascular system. Cardiovascular risk factors and chronic cardiovascular conditions are prevalent among patients affected by COVID-19 and associated with adverse outcomes. However, whether pre-existing cardiovascular disease is an independent determinant of higher mortality risk with COVID-19 remains uncertain. Acute cardiac injury, manifest by increased blood levels of cardiac troponin, electrocardiographic abnormalities, or myocardial dysfunction, occurs in up to ~60% of hospitalized patients with severe COVID-19. Potential contributors to acute cardiac injury in the setting of COVID-19 include (1) acute changes in myocardial demand and supply due to tachycardia, hypotension, and hypoxemia resulting in type 2 myocardial infarction; (2) acute coronary syndrome due to acute atherothrombosis in a virally induced thrombotic and inflammatory milieu; (3) microvascular dysfunction due to diffuse microthrombi or vascular injury; (4) stress-related cardiomyopathy (Takotsubo syndrome); (5) nonischemic myocardial injury due to a hyperinflammatory cytokine storm; or (6) direct viral cardiomyocyte toxicity and myocarditis. Diffuse thrombosis is emerging as an important contributor to adverse outcomes in patients with COVID-19. Practitioners should be vigilant for cardiovascular complications of COVID-19. Monitoring may include serial cardiac troponin and natriuretic peptides, along with fibrinogen, D-dimer, and inflammatory biomarkers. Management decisions should rely on the clinical assessment for the probability of ongoing myocardial ischemia, as well as alternative nonischemic causes of injury, integrating the level of suspicion for COVID-19. (Am Heart J 2020;226:29-44.)

Coronavirus disease 2019 (COVID-19) has affected more than 2 million individuals worldwide.[1] Although COVID-19 predominantly disrupts the respiratory system, there is accumulating experience that the disease, particularly in its more severe manifestations, also affects the cardiovascular system.[2-4] Therefore, an understanding of how COVID-19 may influence the cardiovascular system is important for both cardiovascular practitioners and researchers. This review synthesizes the clinical evidence published to date on the cardiovascular complications of COVID-19, emerging perspectives on their pathophysiology, and evolving best practices for clinical management.

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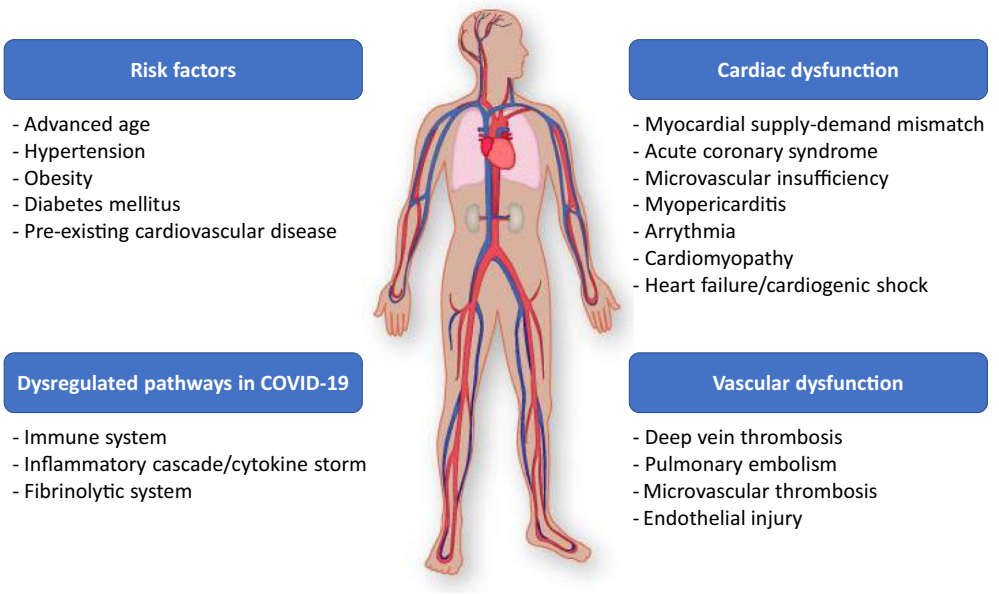
The virus

Coronaviruses (CoV) belong to a family of viruses that account for 10%-30% of all upper respiratory tract infections.[5] The virions are large, enveloped, single-stranded RNA viruses responsible for previous epidemics as well as the common cold. In 2002, severe acute respiratory syndrome (SARS)-CoV infected at least 8,000 individuals, with ~30% of patients requiring mechanical ventilation and ~10% of cases suffering a fatal outcome.[6] Middle East respiratory syndrome (MERS)-CoV, which was first reported in 2012 and has largely been confined to Saudi Arabia, infected greater than 2,500 patients with a case fatality rate of 35%.[7] SARS-CoV-2, the pathogen that causes COVID-19, most closely resembles the SARS-CoV virus from 2002 and has been suspected to have initially been transmitted from bats as a natural reservoir through an intermediate animal host.[8] It gains entry to human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor through a transmembrane surface spike (S) glycoprotein on the viral envelope.[9]

The transmission of the virus is thought to be primarily through large respiratory droplets and contact with contaminated fomites that then result in self-contamination of the eyes, nose, or mouth.[10] Fecal-oral transmission may also be possible but has not been verified

Figure 1



The interplay of COVID-19 and cardiovascular disease includes the common presence of underlying cardiovascular risk factors and conditions as well as the acute consequences of COVID-19.

to be clinically important.[11-13] Whereas SARS-CoV and MERS-CoV were largely transmitted through symptomatic patients, SARS-CoV-2 appears to also be transmitted by asymptomatic individuals. At least 1 study from Asia with extensive contact tracing identified 7 clusters of cases for which spread of the virus occurred 1-3 days prior to symptom development in the source patient. In addition, it has been estimated that prior to travel restrictions in China, 86% of infections were undocumented—meaning undiagnosed and not reported.[14]

A study comparing the stability of SARS-CoV-2 and SARS-CoV found these virions to be stable in aerosols for hours (half-life ~1 hour) and on plastic and metal surfaces for up to 72 hours (half-life ~7 hours).[15] Moreover, the National Institute of Infectious Disease in Japan reported detection of SARS-CoV-2 RNA on surfaces in the cabins of a cruise ship with infected passengers up to 17 days after they were vacated.[16] Studies from the early stages of the epidemic in China, prior to implementation of full mitigation strategies, estimated a basic reproductive number (R_o) of 2.38 for SARS-CoV-2, meaning that every infected individual will, on average, spread the virus to 2 to 3 other individuals.

It has been proposed that COVID-19 progresses through several stages in its disease course.[8,17] The first stage is viral infection during which constitutional symptoms, such as fever and cough, predominate. The second stage is characterized by direct viral cytotoxic effects, particular those in the respiratory tract, leading to respiratory failure and potentially acute respiratory distress syndrome. The third and final stage, which is of particular concern to cardiologists, is thought to be mediated by a hyperinflammatory response to the virus causing systemic effects, including those on the cardiovascular system.

Pre-existing cardiovascular disease and COVID-19

Cardiovascular risk factors and chronic cardiovascular conditions are prevalent among patients affected by COVID-19 and associated with adverse outcomes (Figure 1). In a report from the Chinese Center for Disease Control and Prevention involving 72,314 patients, baseline age, hypertension, diabetes mellitus, and known coronary artery disease were associated with adverse outcomes in COVID-19. In a survey by the Chinese Center for Disease Control and Prevention, among patients diagnosed with COVID-19, 13% had hypertension, 5% had diabetes mellitus, and 4% had a history of cardiovascular disease.[18] In this same study, among patients who died, 40% had hypertension, 20% had diabetes, and 22% had pre-existing cardiovascular disease. Of these and a broad group of other comorbidities, cardiovascular disease was associated with the highest case fatality rate (10.5%). Several smaller, peer-reviewed case series ranging in size from ~100 to 1,000 hospitalized patients have reported similar results, with higher rates of older age, hypertension, diabetes, and cardiovascular disease in patients with more severe manifestations of

COVID-19.[3,4,19,20] However, whether pre-existing cardiovascular disease is independently associated with higher mortality risk with COVID-19 remains uncertain. In a study of 191 patients, only older age, elevated D-dimer, and a higher admission Sequential Organ Failure Assessment score were independently associated with mortality.[4] Thus, the observed unadjusted associations between hypertension, diabetes, and coronary artery disease with worse outcomes in COVID-19 may, in fact, predominantly be a reflection of the higher prevalence of these diseases with increasing age.

Angiotensin-converting enzyme-2 receptor

In addition to these epidemiological observations, an understanding of CoV biology, including SARS-CoV-2 entry into cells via transmembrane ACE2, has also raised the possibility of an increased risk for patients with certain underlying cardiovascular conditions. In animal models, ACE2 is upregulated with hypertension and with ACE inhibition,[21] theoretically creating an increased susceptibility to CoV infection.Preclinical studies, on the other hand, suggest that ACE2 may be protective. Genetic inactivation of ACE2 of ACE2 allowed for severe lung injury in avian-influenza challenged mice and reconstitution of ACE2 mitagated the observed injury.[22] These considerations[10] were amplified by social media and led to concern in the medical community about the use of ACE inhibitors, angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors in patients at risk for COVID-19. However, most major international cardiology professional societies, including the American College of Cardiology (ACC), American Heart association, Heart Failure Society of America, and European Society of Cardiology, have determined that, at present, the available data are insufficient to indicate that use of these agents increases the risk of infection with SARS-CoV-2 and have issued recommendations that patients being treated with ACE/ARB/angiotensin receptor-neprilysin inhibitors should continue regardless of COVID-19 risk or infection.[23,24] Furthermore, there are currently 2 ongoing studies testing the hypothesis that the ARB losartan might be effective in the treatment of nonhospitalized (NCT04312009) and hospitalized patients with COVID-19 (NCT04311177). Although this area is the subject of ongoing investigation, for the time being, experts advise that taking patients with heart failure or past myocardial infarction off of these medications could lead to adverse outcomes and clinical decline.[25]

Cardiovascular complications of COVID-19

Acute cardiac injury

Acute cardiac injury, manifested by increased blood levels of cardiac troponin, electrocardiographic abnormalities, or myocardial dysfunction, appears to be prevalent in subgroups of hospitalized patients with COVID-19.[2-4,26] However, both the epidemiology across the clinical spectrum of patients with COVID-19 and the mechanisms of acute injury remain uncertain.

In one of the first reports to include measurement of cardiac troponin, Zhou et al found that in a series of 191 cases with laboratory-confirmed COVID-19, 17% (n = 33) developed acute cardiac injury.[4] Nonsurvivors had significantly higher blood levels of high-sensitivity cardiac troponin I (hsTnI) levels on admission (median 22.2 ng/L [interquartile range 5.6-83.1]) when compared with the levels in survivors (3 ng/L [1.1-5.5]). Notably, in this small cohort with serial samples, among patients who did not survive, a pattern of increasing hsTnI concentration was observed at approximately day 13 from illness onset, whereas troponin remained below reference range for individuals who survived.[26] These investigators speculated that acute coronary syndrome in the setting of an acute inflammatory state was a cause of injury and cited a pathologist's examination of a patient who died of COVID-19 and had evidence of acute myocardial infarction.

Two single-center studies from academic hospitals in Wuhan, China, also described this clinical finding.[2,26] In a retrospective cohort of 416 patients with laboratory-confirmed COVID-19, Shi et al reported that 19.7% (n = 82) had evidence of myocardial injury as defined by an hsTnI value greater than the 99th percentile reference limit.[2] In-hospital mortality was 51.2% (42 of 82) among patients with myocardial injury compared with 4.5% (15 of 335) among patients without myocardial injury. Furthermore, the mortality rate was associated with the magnitude of troponin elevation. Similarly, Guo et al observed that among 187 patients hospitalized with COVID-19, 52 (27.8%) exhibited myocardial injury as demonstrated by elevation of cardiac troponin T (cTnT).[26] In-hospital mortality was more than 6-fold higher in patients with elevated cTnT levels than in patients with normal cTnT levels (59.6% vs 8.9%). Moreover, patients with underlying cardiovascular disease and increased cTnT levels comprised a subgroup with even higher mortality (69.4%). In contrast, patients with underlying cardiovascular disease without cTnT elevation experienced a more favorable prognosis (mortality 13.3%), albeit still higher than patients without CVD or elevated cTnT (mortality 7.6%). In this study, cTnT levels were statistically significantly correlated with the blood concentrations of C-reactive protein (CRP) (r^2 = 0.281) and N-terminal pro–B-type natriuretic peptide (NT-proBNP, r^2 = 0.376); suggesting a link to the degree of systemic inflammation and myocardial wall stress. In both studies, patients with evidence of myocardial injury were also older with a higher prevalence of coronary heart disease, cerebrovascular disease, chronic heart failure, chronic renal failure, chronic obstructive pulmonary

disease, hypertension, and diabetes.[2,26] A recent case series from New York details their experience with 18 patients presenting with ST-segment elevation on electrocardiography (ECG).[27] In this series, 14 (78%) had focal ST elevations, 8 (57%) had a reduced left ventricular ejection fraction, 5 (62%) had regional wall-motion abnormalities on echocardiography, and 6 (33%) were found to have obstructive coronary disease on coronary angiography. In this series, 72% of patients presenting with ST elevation on ECG died in hospital.

In aggregate, these data suggest that acute myocardial injury may be an important marker of disease severity and adverse prognosis in COVID-19. However, the mechanism(s) underlying this association remains unclear and plausibly multiple in etiology (Figure 2). Potential contributors to acute cardiac injury in the setting of COVID-19 include (1) acute changes in myocardial demand and supply due to tachycardia, hypotension, and hypoxemia resulting in type 2 myocardial infarction; (2) acute coronary syndrome due to acute atherothrombosis in a virally induced thrombotic and inflammatory milieu; (3) microvascular dysfunction due to diffuse microthrombi or vascular injury; (4) stress-related cardiomyopathy (Takotsubo syndrome); (5) nonischemic myocardial injury due to a hyperinflammatory cytokine storm; or (6) direct viral cardiomyocyte toxicity and myocarditis.[8] In the setting of critical illness, these possible contributors can be very difficult to distinguish on clinical grounds. Moreover, treatment is likely to vary substantially depending on whether the suspected etiology is coronary plaque rupture or a combination of oxygen supply-demand mismatch and myocytotoxic effect of pathogens, endotoxins, cytokines, or reactive oxygen radicals induced by infectious processes.[28]

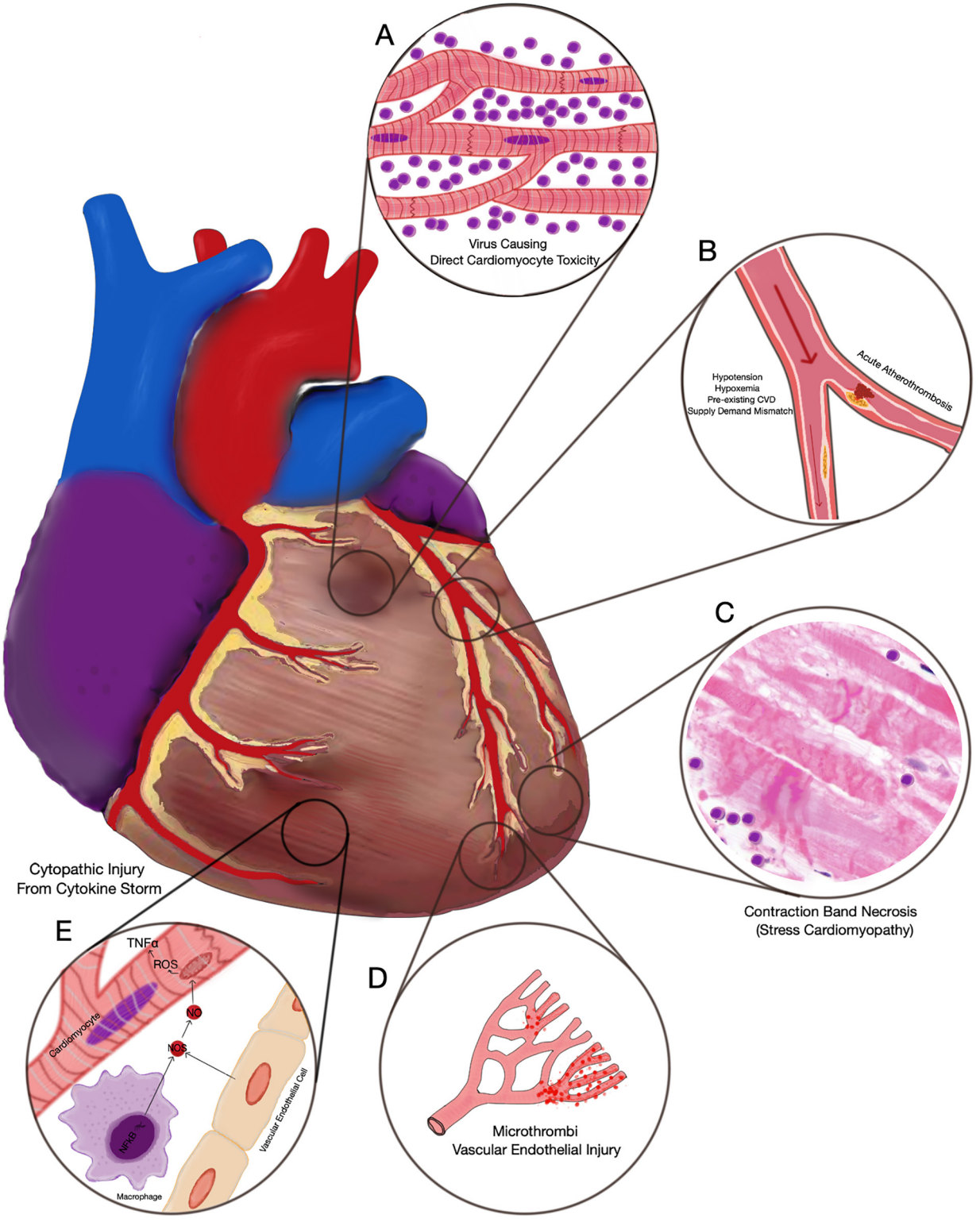
In terms of management of these patients, the decisions should rely on the clinical assessment for the probability of ongoing myocardial ischemia, as well as alternative nonischemic causes of injury, integrating the level of suspicion for COVID-19. For example, according to a recent statement by the Society for Cardiovascular Angiography and Interventions, patients presenting with presumed ST-elevation myocardial infarction (STEMI) should be treated with primary percutaneous coronary intervention (PCI) unless there is a heightened concern for the prevalence of COVID-19 causing systematic and infrastructural delays in care.[29] In the latter situation, it may reasonable to consider fibrinolytic therapy in a low-risk hemodynamically stable patient with STEMI if there is a limitation in availability for PCI due to stressed resources. However, at the present time, primary PCI should be used for the majority of STEMIs. In the case of suspected non-STEMI, efforts should be taken to try to differentiate between an occlusive event and a demand process with tools such as electrocardiogram, echocardiogram, and coronary computed tomography angiography. The Society for Cardiovascular Angiography and Interventions statement also proposed that it is reasonable to consider deferring invasive management, especially if the patient is hemodynamically stable. Coronary angiography, when performed, may also reveal the absence of critical epicardial disease, leading to alternative diagnoses, including Takotsubo syndrome or acute myocarditis.[30]

There is intense scientific and clinical interest in determining the underlying etiology of acute myocardial injury in COVID-19. Epidemiologic and clinical studies of influenza have demonstrated that patients with underlying coronary artery disease and risk factors for atherosclerosis have an increased risk of developing an acute coronary syndrome during acute infections.[31,32] In addition, case reports have described viral myocarditis among COVID-19 patients, although none was confirmed by biopsy.[33,34] Furthermore, patients with general critical illness commonly have elevated troponin levels in the absence of obvious ischemia and are at increased risk of death.[35] The complex relationship between direct deleterious cardiovascular effects specific to SARS-CoV-2 and the cascade effects of the host immune response needs to be further elucidated. Mechanisms for myocardial injury and dysfunction in the setting of severe inflammation and cytokine storm are not currently well defined and include direct myocyte depression as a result of the inflammatory milieu as has been reported in sepsis-induced cardiomyopathy. Animal studies show that elevated cytokines and inflammatory mediators like tumor necrosis factor (TNF)-α and interleukin (IL)-6 lead to decreased contractility, possibly mediated through calcium-dependent pathways.[36-38]

Pericarditis and myocarditis

Myocarditis and pericarditis are potential cardiovascular manifestations of COVID-19, although available evidence is mixed and largely based on single-patient case reports.[33,34,39] A case report from Hu et al reports the evaluation of a 37-year-old man in China who presented with chest pain, dyspnea, and diarrhea and was found to have fulminant myocarditis with acute elevations in cTnT (>10,000 ng/L) and NT-proBNP (>20,000 ng/L) and left ventricular ejection fraction (LVEF) of 27%, with clean coronaries on computed tomography coronary angiography. He was treated with intravenous immunoglobulin (IVIG) and methylprednisolone for immunosuppression, along with supportive care with vasopressors and diuretics, and ultimately had recovery of LV function (LVEF 66%) and improved biomarkers.[33] A subsequent case report from Northern Italy described a 53-year-old woman with confirmed SARS-CoV-2 infection who presented with fatigue, elevated cardiac biomarkers, ECG changes, and a depressed LVEF to 40% with diffuse hypokinesis. A

Figure 2



Representation of the possible mechanisms of acute myocardial injury related to COVID-19. **A**, Myocarditis; (**B**) type 2 MI (left) and type I MI (right); (**C**) contraction bands in stress cardiomyopathy; (**D**) microvascular dysfunction from microthrombi and endothelial injury; and (**E**) cytopathic injury in cytokine storm.

cardiac magnetic resonance imaging showed increased wall thickness, diffuse biventricular hypokinesis, and diffuse late gadolinium enhancement involving most of the myocardium. Notably, her CRP was never elevated above the reference range, and she never suffered from respiratory failure. She was treated with antivirals, including lopinavir/ritonavir, and intravenous methylprednisolone (1 mg/kg daily for 3 days), and on day 6, a repeat echocardiogram showed partial recovery of her LVEF. This report suggests diffuse myocardial inflammation in some cases rather than secondary inflammatory myocardial suppression. Other coronaviruses, including MERS-CoV, have been reported to cause acute myocarditis and heart failure.[40] It remains possible that, in some cases, SARS-CoV-2 causes myocardial dysfunction through viral myocarditis; however, at the point of this writing, pathological evaluation of suspected cases of COVID-19–associated myocarditis, including the possibility of viral entry into cardiomyocytes, is extremely limited. In a case report of a 69-year-old woman presenting with COVID-19 and cardiogenic shock, endomyocardial biopsy revealed coronavirus particles within cytopathic interstitial cells of the myocardium but not in myocytes or endothelial cells.[41] In a 43-year-old woman with COVID-19 and ST elevation with mild left ventricular dysfunction, endomyocardial biopsy demonstrated diffuse T-lymphocytic inflammatory infiltrates with interstitial edema and limited foci of necrosis without SARS-CoV-2 within the myocardium, rendering a final diagnosis of a virus-negative lymphocytic myocarditis.[42] The coronary microvasculature and endothelium may be at risk for viral entry due to ACE2 expression on these vascular cells. In fact, a pathologic study showed direct evidence of viral invasion and resulting apoptosis in epithelial cells of various organs using electron microscopy.[43]

Heart failure and cardiogenic shock

Heart failure and cardiogenic shock appear to be important causes of morbidity and mortality in COVID-19. In a study of 191 patients with confirmed COVID-19 from 2 Chinese hospitals, 23% (n = 44) of patients had a clinical diagnosis of heart failure.[4] Of the patients who died during the study, 52% (n = 28) had developed heart failure versus 12% (n = 16) with heart failure among survivors ($P < .0001$).[4] In another retrospective case series of 150 patients with COVID-19 from 2 Chinese institutions, 33% (n = 22) of deaths were attributed to respiratory failure with myocardial damage or heart failure, with an additional 7% reported as heart failure without respiratory failure.[44] In a clinical review of these deaths, the researchers suggested that fulminant myocarditis may have been the etiology of the heart failure; however, no additional diagnostic details were included. Other potential causes of myocardial dysfunction have been discussed in an earlier section of this review. Some experts have speculated that the heart failure syndrome seen in COVID-19 is mediated predominantly through systemic inflammation and cytokine storm.[17] This theory is grounded in the reports from several studies that have shown markedly elevated inflammatory markers including IL-6, D-dimer, and lactate dehydrogenase (LDH) in patients with severe COVID-19.[3,4] Within this construct, treatment with anti-inflammatory therapies, including antagonists of IL-6, warrants scientific interest and is discussed in a subsequent section of this review.

At the time of this writing, only case reports have described the use of mechanical circulatory support devices in patients with cardiogenic shock as a complication of COVID-19.[30] Venovenous extracorporeal membrane oxygenation (ECMO) is a treatment for refractory respiratory failure, and venoarterial ECMO may be used when the patient is also in need of circulatory support.[45] However, it is unknown whether particular populations of patients respond better to therapy with ECMO than others and what criteria are best used for careful selection of patients who are most likely to benefit in the present resource-constrained environment. Additionally, the time course for possible recovery and successful decannulation strategies from ECMO have not been well described at this time.

Thrombosis/venous thromboembolic disease

Diffuse thrombotic disease is an emerging concern in COVID-19. Other respiratory viral illnesses have been reported to predispose to patients to venous thromboembolism (VTE).[46] Also, in the prior experience with SARS, autopsies showed fibrin thrombi in 85% of cases, with 71% of these associated with pulmonary infarction.[47] It is plausible that SARS-CoV-2 infection also increases VTE risk. A preliminary report identified microthrombi in the pulmonary vasculature in an autopsy of a patient who expired from COVID-19.[48] Another study showed that patients admitted with COVID-19 have high clinical risk scores for thromboembolic events.[49] An early report of thromboembolic events in COVID-19 from a case series of all patients with proven COVID-19 pneumonia that were admitted to any of 3 ICUs in the Netherlands found 31 thromboembolic events in this cohort (n = 184), of which most were pulmonary embolisms (n = 25).[50] Of note, all of these patients were reportedly receiving pharmacological prophylaxis with low–molecular weight heparin, albeit there was underdosing relative to typical dosing at US hospitals in 2 of the 3 centers involved.[50] Changes in coagulation parameters in patients hospitalized with COVID-19 are well documented, with remarkable elevation in D-dimer.[3,4] In one of the largest retrospective studies to date of hospitalized patients with COVID-19 (n = 191), nonsurvivors had a more pronounced increase in D-dimer levels during the course of their disease, and

increased levels (>1 g/L) predicted higher adjusted odds of in-hospital death (odds ratio 18.4, 95% CI 2.6-128.6, P = .003).[4] In another retrospective study (n = 183) comparing COVID-19 survivors versus nonsurvivors, nonsurvivors were shown to have higher D-dimer and fibrin degradation product levels on admission.[51] These differences became more accentuated during serial daily measurements, and by later stages, 71.4% of nonsurvivors met criteria for disseminated intravascular coagulation.[51] This profile of elevated breakdown of fibrin products has also been previously described in hospitalized SARS.[52] The presence of antiphospholipid antibodies was reported in 3 patients with severe COVID-19 and multiple cerebral infarctions (including 1 with concurrent critical limb ischemia). However, the report did not account for other therapies that are known to cause preanalytical challenges in the interpretation of these studies such as blood transfusions. The role of antiphospholipid antibodies in the pathogenesis of thromboembolism remains unclear.[53]

The mechanisms involved in possible thrombotic complications in COVID-19 are uncertain. The regulation of pro- and antithrombotic pathways is complex and contingent on both host and pathogen-related properties.[46] Specific mechanistic studies with SARS-CoV-2 are still lacking, but a prior study of SARS-CoV demonstrated that infection of mice increases proinflammatory (IL-1B, TNF-α, and IL-6) and profibrotic (transforming growth factor B, connective tissue growth factor, and platelet-derived growth factor) cytokine transcripts as well as upregulates genes associated with induction of a procoagulant state and other fibrinolysis pathway components.[54]

Medically ill patients with COVID-19 should receive adequately dosed pharmacological prophylaxis for VTE and receive systemic anticoagulation for established VTE according to guideline recommendations.[55] Given interaction of antiviral therapies with liver function, some academic centers have developed guidelines that suggest to switch direct oral anticoagulants or warfarin to systemic heparin.[56] At least 1 trial of prophylactic antithrombotic therapy for patients with COVID-19 started in early April 2020 (NCT04333407).

Arrhythmias

One case series reported the occurrence of arrhythmias of unspecified type in 17% of hospitalized patients with COVID-19 (n = 23 of 138 total), with higher rate in ICU patients (44%, n = 16) compared with non-ICU patients (7%, n = 7).[3] Another case series of 187 hospitalized patients reported that sustained ventricular tachycardia or ventricular fibrillation occurred in 5.9% (n = 11) of patients. Influenza is also known to precipitate arrhythmias, particularly atrioventricular block and ventricular fibrillation.[57] The causal mechanism is unclear but, analogously to acute cardiac injury, could be secondary to myocarditis, myocardial stress, or ischemia.

Possible pharmacotherapy for COVID-19

At the time of this writing, there are no pharmacotherapies specifically approved for the management of SARS-CoV-2 or the complications of COVID-19. However, in addition to the supportive management described in the section that follows, clinical consideration has been given to off-label use of medications directed toward the virus itself (Table I) by targeting endocytosis of the virus, such as with hydroxychloroquine; by RNA chain termination using antiviral agents such as remdesivir, galidesivir, favipiravir, and ribavirin; or by inhibiting protein synthesis using lopinavir/ritonavir.[58-62] Other efforts have been directed toward modulation of the host's inflammatory responses, using agents such as corticosteroids, tocilizumab, sarilumab, interferon-γ, IVIG, and convalescent serum from patients recovered from COVID-19.[58-60] However, these agents have the potential for deleterious side effects, including cardiac effects such as QT prolongation, cardiomyopathy, or fluid retention. Therefore, while awaiting further data, in our view, all patients with COVID-19 should be considered first for eligibility for participation in a clinical trial before being entertained for the off-label use of antiviral and anti-inflammatory therapies that are experimental in this population. More than 500 trials are ongoing testing novel or repurposed potential therapeutics for SARS-CoV-2. A listing of selected randomized trials is provided in Table II.

Remdesivir

Remdesivir, an adenosine analogue, was initially developed for treatment of Ebola virus infection. It binds to the active site on the RNA-dependent RNA polymerase of viral RNAs, causing premature termination of RNA replication. It has been shown to inhibit viral replication of SARS-CoV, MERS-CoV, and SARS-CoV-2 in in vitro studies.[63-65] Remdesivir improved the outcome of treatment of MERS-CoV infection in a nonhuman primate model based on clinical signs and viral load in lung tissues.[66] There are also case reports of using remdesivir in humans.[67] Two clinical trials in China, 1 in patients with mild and moderate symptoms (NCT04252664) and 1 in patients with severe symptoms (NCT04257656), have been terminated because of lack of patient enrollment with improved control of the epidemic in that country. Several trials are still ongoing in the United States (NCT04292899, NCT04292730). In a cohort of 61 hospitalized patients with oxygen saturation of 94% or less on ambient air who received remdesivir for compassionate use, 57% of patients receiving mechanical

Table I. Potential therapies targeting SARS-CoV-2

Medication	Proposed mechanism	Dosing	Adverse effects	Cardiac monitoring	Key clinical trials
Remdesivir	Inhibits viral RNA-dependent RNA polymerase; reduces viral replication	200 mg on day 1, then 100 mg daily for 5-10 d	Limited data; reports of hypotension, nausea, vomiting; elevation of liver enzymes.	Monitor hemodynamics with infusion	NCT04292899, NCT04292730, NCT04315948, NCT04280705
Lopinavir-ritonavir	Inhibits 3-chymotrypsin–like protease; reduces viral replication	400/100 mg twice daily for up to 14 d	Nausea, vomiting, diarrhea, pancreatitis, hepatitis, QTc prolongation	Monitor QTc especially when used with other QT-prolonging agents	NCT04328012
Chloroquine	Inhibits viral entry by interfering with endocytosis; modulates host immune response	500 mg twice daily for 10 d	Nausea, vomiting, hemolysis (G6PD deficient), QTc prolongation, hypoglycemia, retinal toxicity	Monitor QTc especially when used with other QT-prolonging agents	
Hydroxychloroquine	Inhibits viral entry by interfering with endocytosis; modulates host immune response	400 mg BID for 1 d, then 200 mg BID for 4 d	Similar to chloroquine but less common	Monitor QTc especially when used with other QT-prolonging agents	NCT04328467, NCT04341441, NCT04333732, NCT04342169, NCT04334382, NCT04341727, NCT04345692, NCT04335552
Tocilizumab	Binds IL-6 receptor and inhibits IL-6 activation, modulates host immune response	400 mg or 8 mg/kg for 1-2 doses	Increased risks of infection (including tuberculosis), hypertension, increased AST, hypersensitivity, volume retention	Monitor hemodynamics with infusion; monitor volume status	NCT04310228, NCT04346355, NCT04332094, NCT04320615
Sarilumab	Binds IL-6 receptor and inhibits IL-6 activation, modulate host immune response	Per trial protocol	Increased AST, hypersensitivity, increased triglycerides and LDL-C, neutropenia	Monitor hemodynamics with infusion; monitor volume status	NCT04327388, NCT04321993, NCT04345289
Convalescent plasma	Reduces viral replication in host	Per trial protocol	Transfusion reactions	Monitor hemodynamics with infusion	NCT04343755, NCT04348656, NCT04342182

ventilation were successfully extubated, and 13% of the patients died.[68] The absence of a control group is a critical limitation of this preliminary study. Although more comprehensive data on cardiac toxicities have yet to be published, there is a report of hypotension followed by cardiac arrest during a loading dose in a patient being treated for Ebola.[69] Elevation of hepatic transaminases has been reported in patients receiving remdesivir, raising concerns for hepatotoxicity in patients who are already critically ill.[70] Compassionate use of remdesivir outside of clinical trials is limited.[56]

Chloroquine and hydroxychloroquine

Chloroquine has been used as an antimalarial drug since the 1930s. Because of their immunomodulatory properties, chloroquine and its hydroxyl analogue hydroxychloroquine are also used to treat rheumatoid arthritis and systemic lupus erythematous.[56] These drugs have been shown to interfere with endosome-mediated viral entry.[56,72] They have also been shown to decrease proinflammatory cytokines, possibly decreasing the severity of cytokine storms. Chloroquine has been shown to have in vitro antiviral activities against SARS-CoV-2.[63] An initial small, nonrandomized, open-label French study, in which chloroquine and azithromycin appeared to have faster than expected viral clearance, has since been retracted because of methodological issues.[73] In a randomized trial of 62 patients in Shanghai, China, the treatment group (hydroxychloroquine 200 mg twice daily between days 1 and 5) had shorter fever and cough duration.[74] Several larger randomized trials are ongoing in China and the United States that will provide more robust evidence on the efficacy of chloroquine and hydroxychloroquine. Of note, these medications can cause QT prolongation and potential risks for torsades de pointes especially when used concomitantly with other QT-prolonging medications; careful monitoring is warranted. The ACC has suggested protocols for monitoring both in the clinical trials and inpatient and outpatient clinical care settings.[75] Hydroxychloroquine has also been associated with a higher risk of hypoglycemia in diabetes patients.[61] At the time of this writing, one of the randomized trials studying chloroquine (NCT04323527) was stopped early because of a concern for excess arrhythmias.[76]

Table II. Selected trials of pharmacotherapies for COVID-19 prevention or treatment

Trial title	Study type	Population	Intervention	Key primary outcome	N	Clinical trial #
Chloroquine/Hydroxychloroquine						
Prophylaxis						
Pre-exposure Prophylaxis for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial	Randomized, double blind	HCWs at high risk for COVID-19	HCQ once weekly vs HCQ twice weekly vs control	COVID-19–free survival	3500	NCT04328467
Will HCQ Impede or Prevent COVID-19: WHIP COVID-19 Study	Randomized, double blind	No COVID symptoms	HCQ daily vs HCQ weekly vs placebo vs nonrandomized active comparator	Reduction in the number of COVID-19 infections in HCWs	3000	NCT04341441
An International, Multi-site, Bayesian Platform Adaptive, Randomized, Double-blind, Placebo-Controlled Trial Assessing the Effectiveness of Varied Doses of Oral CQ in Preventing or Reducing the Severity of COVID-19 in Healthcare Workers	Randomized, double blind	HCWs without COVID19 symptoms or diagnosis	CQ/HCQ low dose vs mid dose vs high dose vs placebo	Symptomatic COVID; peak severity of COVID19 over study period	55,000	NCT04333732
Outpatients						
HCQ for Outpatients With Confirmed COVID-19	Randomized, open label	Outpatient	HCQ vs placebo	Duration of viral shedding	400	NCT04342169
Hydroxychloroquine vs Azithromycin for Outpatients in Utah With COVID-19 (HyAzOUT): A Prospective Pragmatic Trial	Randomized, open label	Outpatient	HCQ vs azithromycin	Hospitalization within 14 d	1550	NCT04334382
Hospitalized patients						
WU 352: Open-label, RCT of HCQ Alone or HCQ Plus Azithromycin or Chloroquine Alone or Chloroquine Plus Azithromycin in the Treatment of SARS CoV-2 Infection	Randomized, open label	Hospitalized, not on MV	HCQ vs HCQ + azithromycin vs CQ vs CQ + azithromycin	Hours to recovery AND free from MV/death	500	NCT04341727
A RCT of the Safety and Efficacy of HCQ for the Treatment of COVID-19 in Hospitalized Patients	Randomized, open label	$SpO_2 \leq 94\%$, hospitalized	HCQ vs SoC	Clinical status on 7-point ordinal scale at day 15	350	NCT04345692
Pragmatic Factorial Trial of HCQ, Azithromycin, or Both for Treatment of Severe SARS-CoV-2 Infection	Randomized, open label	Hospitalized	SoC vs HCQ vs azithromycin vs HCQ + azithromycin	WHO Ordinal Scale at 14 d	500	NCT04335552
Remdesivir						
A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe COVID-19	Randomized, open label	Hospitalized, $SpO_2 \leq 94\%$ or requiring O_2, not on MV	Remdesivir vs SoC	Odds ratio for improvement on 7-point ordinal scale on day 14	6000	NCT04292899
A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Moderate COVID-19 Compared to Standard of Care	Randomized, open label	Hospitalized, $SpO_2 > 94\%$ on room air	Remdesivir vs standard treatment	Odds ratio of improving on a 7-point ordinal scale on day 11	1600	NCT04292730
Multi-center, Adaptive, Randomized Trial of the Safety and Efficacy of Treatments of COVID-19 in Hospitalized Adults	Randomized, open label	Hospitalized	Remdesivir vs lopinavir/ritonavir vs lopinavir/ritonavir + interferon β1A vs HCQ vs SoC	Percentage of subjects reporting each severity rating on a 7-point ordinal scale at 15 d	3100	NCT04315948
A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for Treatment of COVID-19 in Hosp Adults	Randomized, double blind	Hospitalized	Remdesivir vs placebo	Percentage of subjects reporting each severity rating on an 8-point ordinal scale	440	NCT04280705
Lopinavir						
Comparison Of Therapeutics for	Randomized,	Hospitalized	Lopinavir/ritonavir,	COVID-19 Ordinal	4000	NCT04328012

(continued on next page)

Table II (*continued*)

Trial title	Study type	Population	Intervention	Key primary outcome	N	Clinical trial #
Hospitalized Patients Infected With SARS-CoV-2 In a Pragmatic aDaptive randoMizED Clinical Trial During the COVID-19 Pandemic	double blind		HCQ, losartan, placebo	Severity Scale (NCOSS) at 60 d		
Tocilizumab						
Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019—A Multi-Center, Randomized and Controlled Clinical Trial Study	Randomized, open label	Did not specify	Tocilizumab with favipiravir, tocilizumab, favipiravir	Clinical cure rate	150	NCT04310228
An Open-Label Randomized Multicenter Study to Evaluate the Efficacy of Early Administration of Tocilizumab (TCZ) in Patients With COVID-19 Pneumonia	Randomized, t, open label	Hospitalized	Tocilizumab vs control	ICU care with MV or death	398	NCT04346355
Pilot, Randomized, Multicenter, Open-Label Clinical Trial of Combined Use of Hydroxychloroquine, Azithromycin, and Tocilizumab for the Treatment of SARS-CoV-2 Infection	Randomized, open label	Hospitalized	Tocilizumab + HCQ + azithromycin vs HCQ + azithromycin (control)	In-hospital mortality; need for MV	276	NCT04332094
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia	Randomized, double blind	Hospitalized	Tocilizumab vs placebo	Clinical status assessed using 7-category ordinal scale at day 28	330	NCT04320615
Sarilumab						
An Adaptive Phase 2/3, Randomized, Double-Blind, Placebo Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients With COVID19	Randomized, double blind	Hospitalized	Sarilumab vs placebo	Time to resolution of fever for ≥48 h or D/C (Ph 2); severity on ordinal scale (Ph 3)	300	NCT04327388
Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	Nonrandomized, open label	Moderate to severe COVID19	Lopinavir/ritonavir vs HCQ vs baricitinib vs sarilumab	Clinical status of subject at day 15 on 7-point ordinal scale	1000	NCT04321993
Efficacy and Safety of Novel Treatment Options for Adults With COVID-19 Pneumonia. A Double-Blinded, Randomized, Multi-Stage, 6-Armed Placebo-Controlled Trial in the Framework of an Adaptive Trial Platform	Randomized, double blind		Convalescent serum vs sarilumab vs IV placebo vs HCQ vs baricitinib vs oral placebo		1500	NCT04345289
Convalescent plasma						
Phase IIa Study Exploring the Safety and Efficacy of Convalescent Plasma From Recovered COVID-19 Donors Collected by Plasmapheresis as Treatment for Hospitalized Subjects With COVID-19 Infection	Single group	Hospitalized, moderate symptoms	Convalescent plasma	Mechanical ventilation at 7 d) or death at 30 d	55	NCT04343755
A Randomized Open-Label Trial of CONvalenscent Plasma for Hosp Adults With Acute COVID-19 Respiratory Illness	Randomized, open label	Hospitalized, on supplemental oxygen	Convalescent plasma vs SoC	Intubation or death in hospital	1200	NCT04348656
Convalescent Plasma Therapy From Recovered Covid-19 Patients as Therapy for Hospitalized Patients With Covid-19	Randomized	Hospitalized	Convalescent plasma vs SoC	In-hospital mortality at 60 d	426	NCT04342182

HCW, denotes healthcare worker; HCQ, hydroxychloroquine; CQ, chloroquine; MV, mechanical ventilation; SoC, standard of care.

Lopinavir-ritonavir

Lopinavir is a human immunosuppression virus-1 protease inhibitor that is used in combination with ritonavir to treat human immunosuppression virus infections. During the 2003 SARS pandemic, in an open-label study, lopinavir-ritonavir, ribavirin, and corticosteroid appeared to have lower rate of acute respiratory distress syndrome or death in the treatment group compared with a historical control group who received only ribavirin and a corticosteroid.[77,78] In an open-label, randomized, controlled trial involving 199 seriously ill patients with COVID-19 in China, compared with standard care, treatment with lopinavir-ritonavir did not result in clinical improvement or reduced mortality.[79] Lopinavir-ritonavir causes significant gastrointestinal adverse effects, can cause pancreatitis and hepatitis in patients with pre-existing liver disease, and prolongs the QT interval.[61]

Tocilizumab and sarilumab

Tocilizumab and sarilumab are IL-6 antagonists. Initially approved for treatment of rheumatoid arthritis, tocilizumab is also used for treatment of cytokine release syndrome in patients treated with chimeric antigen receptor T-cell therapy.[80] Previous studies have found increased levels of cytokines, such as IL-6, IL-8, and TNF-α, in patients with SARS and MERS.[81,82] Similar increase in inflammatory markers has also been observed in patients with COVID-19, suggesting cytokine storm as a possible underlying contributor to the end-organ dysfunction seen in this disease.[83] Given these observations, tocilizumab and sarilumab have been proposed as candidate therapies for patients with severe COVID-19. Both medications have been approved for clinical trials (Table I). Tocilizumab has been shown to increase fluid retention and potentially increase lipid profile, but was not found to increase risk of cardiovascular complications in large cohort studies.[84] Both medications can cause immunosuppression and increased risks of serious infections including tuberculosis, hypersensitivity, and increased liver enzymes.[85,86] Sarilumab can also cause decreased neutrophil and platelet counts, and increased low-density lipoprotein and tryglycerides.[86]

Convalescent plasma

Convalescent serum from individuals who have recovered from viral infection has been used to treat patients with acute viral infections, such as Ebola, H5N1, and H1N1, although efficacy results were mixed.[87-90] Convalescent serum was also used during the SARS pandemic and was found to be associated with higher 22-day discharge rate (74% vs 19%, $P < .001$).[91] In a more recent case series, 5 critically ill patients with COVID-19 treated with convalescent serum showed clinical improvement; however, larger studies with more rigorous design are needed.[92] Clinical trials are ongoing to test the feasibility and efficacy of using convalescent plasma (Table I).

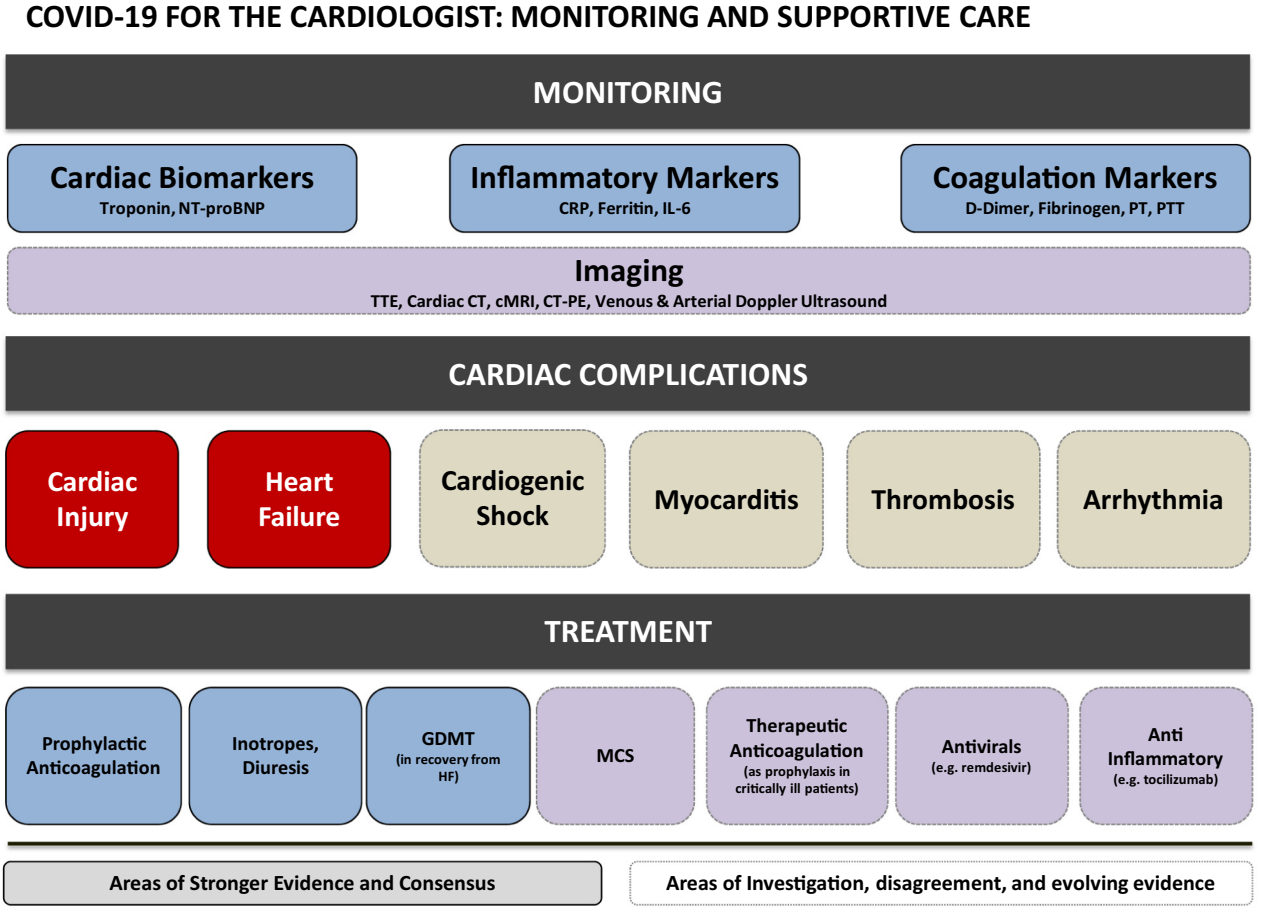
Supportive management and cardiovascular assessment of patients with COVID-19

Cardiologists involved in the care of patients with COVID-19 face a wide range of care decisions in the context of a rapidly evolving but, as yet, modest evidence base (Figure 3). In addition to experimental antiviral and anti-inflammatory therapies discussed in the next section of this review, management is focused on supportive care aimed at mitigating the respiratory insufficiency that predominates in COVID-19 as well as the consequences of other end-organ injury resulting from the viral infection.

Key principles for management of respiratory failure in COVID-19 include (1) caution regarding the use of aerosolizing devices for delivery of supplemental oxygen due to risk of viral transmission; (2) low tidal volume mechanical ventilation and high positive end-expiratory pressure; and (3) liberal use of prone ventilation, including consideration of "self-proning" in the nonintubated patient. Guidance from the Surviving Sepsis Campaign COVID-19 Subcommittee includes use of nasal cannula when patients' Spo_2 drops below 90%.[93] When respiratory failure worsens beyond the support available by nasal cannula, the use of either high-flow nasal cannula or noninvasive positive pressure ventilation must be balanced against the risk of aerosolization, and thus, both have been classified as a weak recommendation based on low-quality evidence and risk. Use of a nonrebreather or Venturi masks is believed to maximize oxygen delivery without significant aerosolization. In many centers, patients are intubated earlier in the disease course, which may help avoid emergent intubation and excess risk to health care workers.[94] Once intubated, adherence to general principles of ventilation for patients with acute respiratory distress syndrome is recommended with low tidal volumes (4-8 mL/kg of ideal body weight), inspired fraction of oxygen ≤50% as soon as achievable, and higher positive end-expiratory pressure with the aim to mitigate the risk of high driving pressure (barotrauma) or tidal volumes (volutrauma) and of oxygen-related toxicity.[95]

COVID-19 is known to be a systemic illness with numerous complications other than cardiac. Abnormal liver enzymes are common, but *acute liver injury*, defined as 3 times the upper limit of normal, appears to occur largely as a result of shock and critical illness.[20,96] Acute kidney injury occurs at high rates for those hospitalized with severe manifestations of the disease.[4,8,20] Renal

Figure 3



COVID-19 for the cardiologist: Monitoring for cardiovascular complications and supportive management. *PT*, prothrombin time; *PTT*, partial thromboplastin time; *TTE*, transthoracic echocardiogram; *cMRI*, cardiac magnetic resonance imaging; *CT-PE*, computed tomography pulmonary angiogram; *MCS*, mechanical circulatory support; *GDMT*, guideline-directed medical therapy.

replacement therapy is needed in approximately 5% of patients with COVID-19 admitted to ICUs.[97] For critically ill patients, disseminated intravascular coagulation has been noted, but disturbances of coagulation in most patients with COVID-19 are characterized by a hypercoagulable profile with very high D-dimer and fibrinogen, possibly predisposing patients to macrovascular thrombosis.[50,51] Standard guidelines for anticoagulation for prophylaxis of venous thromboembolism in acute medical illness should be followed assiduously, and in some centers, consideration is given to more intensive prophylactic anticoagulation. Lastly, potential drug-drug interactions between antiplatelet agents and anticoagulants with investigational COVID-19 therapies ought be considered when caring for patients requiring these cardiovascular therapies.[98]

As yet, there are no evidence-based guidelines for monitoring of cardiovascular complications of COVID-19. Because of the observation that patients with COVID-19 with significantly elevated cardiac biomarkers (cardiac troponin, natriuretic peptides, CRP, D-dimer) tend to have worse outcomes, some centers are routinely measuring such biomarkers in a serial manner.[56] This approach is commensurate with the view that prognostic information in trending serial biomarkers may be useful for clinicians in better monitoring and predicting the disease course, helping to triage patients to appropriate level of care and to inform the tailoring of vasoactive agents in shock.[99] In contrast, the ACC published a statement advising against routine testing of troponins and BNP in patients admitted with COVID-19, arguing that these tests should only be used when there is evidence of either myocardial infarction or new heart failure.[100] The routine use of cardiac imaging, including echocardiography, has been challenging for institutions

trying to balance the risk for health care workers exposed to these patients versus the clinical utility of these tests; consequently, clinicians are being advised to use point-of-care ultrasound when possible.[101] Under normal circumstances, in a disease that is known to cause myocardial dysfunction and heart failure, a patient with high cardiac biomarkers and evidence of volume overload would likely prompt a transthoracic echocardiogram; however, in the setting of COVID-19, careful consideration should be given to whether the imaging study will affect management and whether or not a point-of-care ultrasound is applicable as a screening tool. If acute cardiac diseases or complications are identified, treatment for heart failure, cardiogenic shock, and myocarditis should generally follow clinical practice guidelines irrespective of COVID-19, including the use of inotropes and mechanical circulatory support when appropriate in the context of the patient's overall prognosis and availability of resources.[94] Invasive evaluation for suspected ongoing myocardial ischemia has been discussed in an earlier section of this review.

Summary

COVID-19 is more than a respiratory illness; it is now understood to have broad systemic effects, including cardiovascular manifestations (Figure 1). Cardiac injury may occur through possible ischemic and nonischemic mechanisms (Figure 2). Diffuse microvascular and macrovascular thrombosis is emerging as a recognized complication and possibly central pathology of COVID-19. Moreover, with the expanding use of antiviral therapies, medication-induced cardiac toxicity may become increasingly common. Heart failure and cardiogenic shock are known to occur as a result of COVID-19, either by an inflammatory cardiomyopathy or by viral myocarditis, or possibly due to ischemic injury. Protocols for monitoring and treating these entities remain subject to investigation. Although what we know about the epidemiology of COVID-19 has expanded rapidly, additional rigorous investigation is needed to more completely elucidate the cardiovascular complications of COVID-19 and provide guidance for their treatment.

Disclosure

The authors have no relevant disclosures to report.

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