Cardiovascular Pathophysiology, Epidemiology, and Treatment
Considerations of Coronavirus Disease 2019 (COVID-19): A Review

Short Title: Cardiovascular Implications of COVID-19

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The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rapidly evolving, with important cardiovascular considerations. The presence of underlying cardiovascular risk factors and established cardiovascular disease (CVD) may affect the severity and clinical management of patients with COVID-19. We conducted a review of the literature to summarize the cardiovascular pathophysiology, risk factors, clinical presentations, and treatment considerations of COVID-19 patients with underlying CVD. The angiotensin-converting enzyme 2 (ACE2) enzyme has been identified as a functional receptor for the SARS-CoV-2 virus, and is associated with the cardiovascular system. Hypertension, diabetes, and CVD are the most common comorbidities in COVID-19 patients, and these factors have been associated with the progression and severity of COVID-19. However, elderly populations, who develop more severe COVID-19 complications, are naturally exposed to these comorbidities, underscoring the possible confounding of age. Observational data supports international cardiovascular societies’ recommendation to not discontinue ACEi/ARB therapy in patients with guideline indications out of fear for the increased risk of SARS-CoV-2 infection, severe disease, or death. In addition to the cardiotoxicity of experimental antivirals and potential interactions of experimental therapies with cardiovascular drugs, several strategies for cardiovascular protection have been recommended in COVID-19 patients with underlying CVD. Troponin elevation is associated with increased risk of in-hospital mortality and adverse outcomes in patients with COVID-19. Cardiovascular care teams should have a high index of suspicion for fulminant myocarditis-like presentations being SARS-CoV-2 positive, and remain vigilant for cardiovascular complications in COVID-19 patients.
Key Words: SARS-CoV-2, COVID-19, cardiovascular system, cardiovascular disease, treatment considerations, cardiovascular drug interactions, review.

BRIEF SUMMARY

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is rapidly evolving, with important cardiovascular considerations. Here, we highlight the pathophysiology, cardiovascular risk factors, clinical presentations, and treatment considerations for COVID-19 patients with underlying cardiovascular disease (CVD).

ABBREVIATIONS

ACE2 Angiotensin-Converting Enzyme 2
CAD Coronary Artery Disease
CK Creatine Kinase
COVID-19 Coronavirus Disease 2019
CVD Cardiovascular Disease
ECMO Extracorporeal Membrane Oxygenation
Hs-cTnI High-sensitivity Cardiac Troponin I
ICU Intensive Care Unit
SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2
WHO World Health Organization
INTRODUCTION

In late December 2019, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak occurred in Wuhan, China.\(^1\) The World Health Organization (WHO) has declared the coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, to be a public health emergency of international concern which has since been characterized as a pandemic.\(^2\) While COVID-19 patients primarily present with respiratory symptoms, reports are evolving of patients developing significant cardiovascular complications.\(^3\) Several studies have previously found a transient yet pronounced association between lower respiratory tract infections and acute coronary syndromes, suggesting important clinical implications of the SARS-CoV-2 virus.\(^4\)\(^-\)\(^7\)

This review will elucidate the biological underpinnings for COVID-19’s impact on the heart, epidemiological trends related to cardiovascular disease (CVD), cardiovascular society guidelines, and cardiovascular clinical implications characterized in the context of COVID-19 patients. Summarizing and understanding the pathophysiological basis for these changes will have immediate consequences on the clinical management of these patients, prove critical to the development of effective disease modifying treatments, and ultimately reduce mortality.

METHODOLOGICAL CONSIDERATIONS

We narratively reviewed the published literature (including searches in the MEDLINE (via PubMed) database) and grey literature from inception through May 18, 2020. Articles were retrieved using keywords and medical subject heading terms related to COVID-19, severe acute respiratory syndrome coronavirus 2, and the cardiovascular system. Observational studies and articles discussing the cardiovascular pathophysiology, epidemiology, and treatment considerations of COVID-19 were considered relevant for this narrative synthesis. Titles and abstracts were screened, and citations considered potentially eligible were retrieved for full-text
review. References of included articles were also searched for relevance, as were articles of major peer-reviewed journals that were not yet indexed. The grey literature was searched for relevant clinical and epidemiological information via major public health websites including the WHO, Chinese, European, and American Centers for Disease Control and Prevention (CDC), as well as Epicentro (Italy). Extracted epidemiological data included study design, count data for patient cardiovascular comorbidities (smoking, hypertension, diabetes, CVD, coronary artery disease (CAD), atrial fibrillation, congestive heart failure, and cerebrovascular disease) and cardiac biomarker levels. Identified primary articles published by the inclusion date that reported count data for at least one of the cardiovascular comorbidities in COVID-19 positive (clinically diagnosed and/or confirmed by reverse-transcriptase polymerase chain reaction positive testing) adult patients were included in Tables 1 and 2. Abstracts, editorials, conference proceedings, and clinical trial registrations were excluded, as were studies that focused on patient subpopulations (e.g., pediatric or obstetric patients). Only articles published in English language were included. Where studies divided patients into cohorts, count data was pooled to reflect all patients for Tables 1 and 2.

**DISCUSSION/OBSERVATIONS**

**Pathophysiology**

A next-generation sequencing experiment of the SARS-CoV-2 virus revealed that while genetically distinct, the SARS-CoV-2 virus receptor-binding domains are structurally similar to the SARS-CoV-1 (cause of the 2003 global SARS outbreak) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) viruses. Seeing that the SARS-CoV-1 virus uses an external spike subdomain to invade lung alveolar epithelial cells via the angiotensin-converting enzyme 2 (ACE2) surface protein, it has been suggested and proven that the SARS-CoV-2 virus
similarly uses ACE2 as a functional receptor (Figure 1). The high ACE2 expression on lung pneumocytes, structural ligand-receptor interaction of SARS-CoV-2 and ACE2, and lower respiratory tract symptoms that accompany SARS-CoV-2 infection validate ACE2 as the site for SARS-CoV-2 entry and viral replication in humans. This has important clinical implications, seeing that ACE2 is also highly expressed in small intestine, heart, venous endothelial, and kidney tissues. ACE2 functions by degrading Angiotensin II (converted by ACE1 from Angiotensin I) into Angiotensin 1-7 (Ang 1-7), in turn opposing the pressor response of Angiotensin II and inducing a vasodilatory response.

The elevated expression of several cardiac biomarkers has been reported in severe COVID-19 cases. These changes support involvement of the cardiovascular system, which can be explained by the combined effects of several mechanisms (Figure 1). First, the systemic oxidative stress induced by hypoxemia in severe acute respiratory syndromes can directly damage cardiomyocytes, resulting in intracellular acidosis and mitochondrial damage. Second, ACE2 receptors also located in the cardiovascular system can dysregulate the renin-angiotensin-aldosterone (RAAS) system, leading to altered myocardial demand via ventricular remodeling and further induction of cardiomyocyte damage. Third, the cytokine storm induced by the systemic inflammatory response syndrome to COVID-19 has been reported in autopsy findings to result in cardiac interstitial mononuclear inflammatory infiltrates. Finally, these local and systemic effects can induce cardiac microvasculature damage resulting in perfusion defects. In a case report of a COVID-19 patient with cardiogenic shock, endomyocardial biopsy identified viral particles of SARS-CoV-2. However, these particles were in the interstitial space and no viral particles were identified within the cardiomyocytes. In addition, the biopsy showed a low grade of myocardial inflammation which was not proportional
to the degree of left ventricular dysfunction.\textsuperscript{16}

### Clinical Presentation

**Cardiovascular Epidemiology**

Individuals with pre-existing multi-morbidities and COVID-19 are reported to be at higher risk of adverse clinical outcomes.\textsuperscript{24} Of note, hypertension, diabetes, and CVD were consistently found to be the most common comorbidities in COVID-19 patients across all identified studies (Table 1). Albeit these consistently reported correlations, age remains an important confounding variable. Older individuals with COVID-19 are known to suffer a more severe clinical course than younger individuals, and hypertension and diabetes are among the most common co-morbidities in this population. Therefore, it is possible that these associations are confounded by age.

The majority of early COVID-19 studies originate from China. An appreciation of the epidemiological landscape in China prior to the COVID-19 pandemic is important for comparing trends observed in the COVID-19 outbreak. Studies have previously characterized China as having an aging population, where atherosclerotic CVD is the leading cause of death, and the prevalence of hypertension and diabetes is 23.2\% and 10.9\%, respectively.\textsuperscript{25-28} Furthermore, trends in smoking have been consistently high, with a 2013 estimated proportion of current smokers in China being 25.2\%.\textsuperscript{29} The leading causes of years of life lost in China are atherosclerotic CVD, lung cancer, chronic obstructive pulmonary disease, and liver cancer.\textsuperscript{28} Of the 14 identified observational studies from China, eight reported on the prevalence of concomitant CVD in COVID-19 patients which ranged between 4.0-40.4\% (Table 1; the upper estimate combined CVD with cerebrovascular disease). The proportion of COVID-19 patients with underlying hypertension ranges between 9.5-50.0\% (Table 1; the upper estimate is in fatal
COVID-19 cases), as does the proportion with comorbid diabetes range between 7.4-25.0%.

Furthermore, 3.8-14.6% of COVID-19 patients are reported to have a smoking history. Finally, 2.5-18.5% (upper estimate is in fatal COVID-19 cases) of COVID-19 patients are reported to have pre-existing CAD. While this greatly informs the clinical picture of COVID-19 patients in China, it remains unclear due to wide and overlapping estimates whether CVD patients are disproportionately diagnosed with COVID-19.

**Pre-existing CVD and COVID-19 Disease Severity**

Underlying cardiovascular risk factors and disease have been associated with the severity of COVID-19 progression, and are closely linked to age. The population-wide serology-informed infection fatality risk (IFR) for SARS-CoV-2 infection has been estimated at 0.64% (95% credible interval: 0.38-0.98), with older age groups contributing the vast majority of fatalities. Although intervals vary between studies, within-study data suggests hypertension is a clinical condition associated with COVID-19 severity. In a bivariate cox regression analysis, hypertension was associated with a significant 82% increased risk in the development of acute respiratory distress syndrome (ARDS) in COVID-19 patients compared to non-hypertensive COVID-19 patients (Hazard Ratio (HR): 1.82; 95% CI: 1.13-2.95). Similarly, diabetes was associated with a significant 134% increased risk of COVID-19 patients developing ARDS compared to non-diabetic COVID-19 patients (HR: 2.34; 95% CI: 1.35-4.05), as well as a nonsignificant 58% increased risk in mortality (HR: 1.58; 95% CI: 0.80-3.13). Fang et al. propose that the increased expression of ACE2 seen in type I and II diabetics and the therapeutic administration of ACEis/ARBs in hypertensive patients contributes to increased viral entry and COVID-19 disease severity. However, further studies are necessary as these hypotheses are not yet clinically supported. The underlying microvascular disease in diabetes may also predispose
COVID-19 diabetic patients to further microvascular damage and cardiac injury hypothesized to be induced by the SARS-CoV-2 virus. CAD has also been shown to have an increased prevalence in COVID-19 patients. Between 9-25% of COVID-19 patients admitted to the intensive care unit (ICU) had underlying CVD, whereas CVD was found in only 2-11% of non-ICU patients. While precise pathophysiological mechanisms are not yet described, these results suggest that underlying CVD should be considered in the prognostication and prioritization of treatment for COVID-19 patients.

Baseline clinical data has also been published on severe COVID-19 patients primarily outside of China, whom were either hospitalized, critically ill, or died (Table 2). Seven observational studies were identified, three of which reported data from Italy, and four from the United States of America (USA) (Table 2). Data reported by the COVID-19 Surveillance Group indicated that 68.1% (1,940/2,848) of COVID-19 non-survivors in Italy had underlying hypertension. Further data from Italy reported the prevalence of atrial fibrillation to range between 22.5-24.5% in COVID-19 patients that had died. In a USA observational study of 5,700 hospitalized COVID-19 patients, hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) were the most common comorbidities. Hypertension was consistently found to be the most prevalent comorbidity in larger USA studies (range between 43.5-56.6%).

**Cardiac Biomarkers and COVID-19 Disease Severity**

Of the 21 primary studies identified, 11 reported data on elevated cardiac biomarkers in relation to COVID-19. Of 3,533 patients hospitalized with COVID-19 in the New York City area, 22.6% has a troponin level above the test-specific upper limit of normal. Troponin T elevations were more likely in patients with underlying CVD (54.5%) compared to those without CVD (13.2%), and were also significantly associated with a poor clinical
High-sensitivity cardiac troponin I (hs-cTnI) levels were repeatedly elevated among severely-ill COVID-19 patients compared to non-severely ill COVID-19 patients (median estimates range between 3.3-30.3 pg/mL for non-survivor/ICU patients versus 3.0-5.1 pg/mL for survivors/non-ICU patients). Between 31-46% of non-survivors were above the hs-cTnI 99th percentile upper reference limit (>28 pg/mL) versus only 1-4% in survivors. One study found the mortality rate during hospitalization in COVID-19 patients with elevated Troponin T and underlying CVD to be 69.4%. In a univariate analysis, log hs-cTnT and log N-terminal-pro-B-type natriuretic peptide were found to be statistically significant independent predictors of progression to severe disease in COVID-19 patients. Several studies have also demonstrated a trend of increased creatine kinase (CK) levels in COVID-19 non-survivors versus survivors, however these findings were nonsignificant in most cases. One study has demonstrated CK above 185 U/L to be significantly increased in non-survivors (21%) versus survivors (9%) (p=0.038). Whereas 59% of non-survivors developed acute cardiac injury, this outcome only occurred in 1% of survivors (p<0.0001). This was similarly observed for heart failure, which 52% of non-survivors developed compared to only 12% of survivors (p<0.0001). Studies have similarly shown that more severe COVID-19 presentations had elevated D-dimer levels and pro-thrombin time, suggestive of a hypercoagulable state. This is consistent with the immune-mediated multisystem inflammatory syndrome associated with COVID-19 which has been documented in children and adolescents.

**Treatment Considerations**

**Cardiovascular Protection**

In light of CVD patients being more likely to develop severe symptoms if infected with the SARS-CoV-2 virus, CVD patients will ultimately account for a large proportion of COVID-
19 deaths.\textsuperscript{17} Trends are consistent with previous coronaviruses,\textsuperscript{49-51} suggesting changes in clinical management should be implemented early in order to minimize the burden of CVD on systemic inflammatory responses. Aside for the systemic inflammatory demand created by COVID-19, the precise biological mechanisms of action of the SARS-CoV-2 virus can theoretically contribute to increased cardiac vulnerability. It is possible that ACE2 sequestering by the SARS-CoV-2 virus and the subsequent downregulation of its expression,\textsuperscript{52} may result in removing the cardioprotective effects of Ang 1-7 which ACE2 is responsible for.

Statins have been suggested as a potential mechanism for cardiovascular protection, especially in COVID-19 patients with underlying CVD, since many may already have poor functional reserve and can rapidly deteriorate when precipitated by the higher metabolic demands of a viral infection like SARS-CoV-2. In addition to regulating dyslipidemias, statins have been recognized for their anti-inflammatory, immunomodulatory, and antithrombotic activity in patients with viral respiratory illnesses.\textsuperscript{53, 54} Randomized controlled trial (RCT) data is conflicting on the use of statins in ventilator-associated pneumonia.\textsuperscript{55, 56} However, beta coronaviruses highly induce the myeloid differentiation primary response 88 (MYD88) signaling pathway, and statins are known stabilizers of this pathway during hypoxia, promoting the innate immune response.\textsuperscript{57, 58} Especially in COVID-19 patients with underlying primary indications, statin therapy should not be discontinued and should be considered for cardiovascular protection in all COVID-19 patients.\textsuperscript{53}

\textbf{ACEi/ARB Controversy}

The continued use of ACE inhibitors (ACEis) and angiotensin receptor blockers (ARBs) in patients with cardiovascular disease and COVID-19 has been met with controversy.\textsuperscript{35, 59, 60} RAAS antagonists act on ACE2 by increasing its cell surface expression, which could
theoretically contribute to increased viral entry, however this has only been demonstrated in animal models.\textsuperscript{61,62} Counterintuitively, maintenance of normal ACE2 levels has protective pulmonary effects and is necessary for combatting inflammatory lung disease.\textsuperscript{63,64} The position of all major cardiovascular societies has been to continue ACEis/ARBs in all COVID-19 patients already prescribed these medications for indications such as hypertension, ischemic heart disease, or heart failure (Table 3).\textsuperscript{65-70} This is consistent with an expert review on the interplay between SARS-CoV-2 and the RAAS system, which highlights insufficient clinical data and potentially beneficial effects during lung injury.\textsuperscript{64} Several large observational studies have since been published reporting that despite the more frequent use of ACEis/ARBs in COVID-19 patients due to underlying CVD, there was no association between ACEi/ARB use and the risk of SARS-CoV-2 infection, COVID-19 clinical severity, or in-hospital mortality among those with a positive SARS-CoV-2 test.\textsuperscript{71-75} While these observational studies are limited by unmeasured confounding, there is reassurance in the consistent findings being independently published. However, RCTs will ultimately be necessary to definitively address these concerns, with several currently underway.\textsuperscript{76,77} Other drugs, such as thiazolidinediones and ibuprofen, have also been suggested to increase ACE2 expression, however reports are limited.\textsuperscript{35}

**Potential Antiviral Interactions with the Cardiovascular System**

The Liverpool Drug Interactions Group has developed a comprehensive evidence evaluation system synthesizing the drug-drug interactions of experimental COVID-19 therapies, which we’ve adapted specifically for cardiovascular drugs (Table 4).\textsuperscript{78} These factors, combined with the higher cardiometabolic demand of COVID-19 patients, can precipitate cardiovascular complications. Cardiovascular care teams should be aware of important drug interactions as the urgent development of COVID-19 disease modifying treatments further evolves.
Several antivirals being evaluated for the treatment of COVID-19 can adversely interact with cardiovascular drugs, and can induce myocardial toxicity, causing or exacerbating existing heart failure.\(^{78-80}\) Albeit observational studies suggesting otherwise and no randomized data supporting its efficacy in COVID-19 patients, hydroxychloroquine and chloroquine are antimalarials that have been proposed for the treatment of COVID-19.\(^{81,82}\) These drugs have known cardiotoxicity manifestations such as corrected QT (QTc) interval prolongation, restrictive or dilated cardiomyopathy, and conduction system abnormalities including atrioventricular and bundle-branch block.\(^{79,80,83-85}\) In a phase IIb RCT of high versus low dosage chloroquine in severe COVID-19 patients, higher dosage chloroquine, especially when taken concurrently with azithromycin and oseltamivir, was found to be unsafe due to increased instances of QTc intervals greater than 500 milliseconds.\(^{86}\) In the high dosage group, two of the 37 patients experienced ventricular tachycardia without torsade de pointes, which is usually facilitated by a prolonged QTc interval, before death.\(^{86}\) In another cohort study of 84 consecutive COVID-19 patients where hydroxychloroquine was administered with azithromycin orally, the QTc interval was significantly prolonged when compared to baseline.\(^{87}\) Several observational studies have described an increased risk of QTc interval prolongation in COVID-19 patients treated with hydroxychloroquine and azithromycin, compared to hydroxychloroquine alone.\(^{88,89}\) Drug-induced cardiac toxicity may be influenced by disease severity, age, and presence of co-morbidities.\(^{87,90}\)

Remdesivir, a nucleoside analogue prodrug that inhibits ribonucleic acid (RNA)-dependent RNA polymerases, has garnered much attention as a promising antiviral for the treatment of COVID-19.\(^{91,92}\) In the National Institutes of Health Adaptive COVID-19 Treatment Trial, hospitalized COVID-19 patients receiving Remdesivir had a 31% faster recovery time than
similar patients who received placebo (p<0.001). Remdesivir has not been characterized to have attributable cardiovascular side effects, although data is still lacking. Additionally, Remdesivir has no known cardiovascular drug-drug interactions aside for a potential interaction with bosentan, which may require a dose adjustment or close monitoring. Dexamethasone, the first treatment to reduce COVID-19-related mortality in critically ill patients, also has several potential interactions with antiarrhythmic, anti-coagulant, anti-platelet, fibrinolytic, and hypertensive diuretic agents. The combination of Lopinavir-Ritonavir has also been proposed, however in the cardiac patient these should be carefully considered due to known QT prolongation effects and limited clinical benefit. Furthermore, this antiviral combination has several drug interactions, and can reduce the effectiveness of clopidogrel and oral anticoagulants (Table 4).

**Cardiac and Intravascular Injury**

The cumulative cardiomyocyte damage and membrane disruption caused by the cardiac injury mechanisms discussed may result in increased hs-cTnI, CK and CK-MB, as well as potential structural remodeling and enlargement observed on chest X-rays, electrocardiograms, and echocardiography. An early study described palpitations among the presenting complaints of COVID-19 patients. Electrocardiogram findings of cardiac arrhythmias have since been reported, and include temporary S1Q3T3 patterns, atrioventricular block, and ST-segment elevation. Throughout the course of disease, malignant arrhythmias including multifocal ventricular tachycardia/ventricular fibrillation have been reported to develop and were associated with higher Troponin T levels. Myocardial injury defined as troponin elevation can be due to target organ damage by hypoxemia, Takotsubo cardiomyopathy, or myocarditis.
suggesting that myocardial injury may play a role in the fatality of some COVID-19 patients. Furthermore, elevated D-dimer and pro-thrombin levels indicate a hypercoagulable state which has been associated with poor outcomes in COVID-19 patients.\textsuperscript{3, 13, 14, 30} Especially in those with underlying CVD, the risks for hemodynamic changes from ischemia and thrombosis that result from this hypercoagulable state are of important clinical concern.\textsuperscript{13} A case-series of young COVID-19 patients presenting with large-vessel stroke has been reported, further supporting coagulopathy and vascular endothelial dysfunction as complications of COVID-19.\textsuperscript{101} Critically ill COVID-19 patients may develop sepsis-induced coagulopathy or disseminated intravascular coagulation, warranting thromboembolic prophylaxis and standard supportive care measures.\textsuperscript{102} The International Society on Thrombosis and Haemostasis interim guidance on coagulopathy in COVID-19 recommends monitoring of fibrinogen in addition to other coagulation markers (platelet count, prothrombin time, and D-dimers) for critically ill patients with COVID-19.\textsuperscript{103} In a retrospective Chinese cohort of severe COVID-19 patients with markedly elevated D-dimer levels or meeting sepsis-induced coagulopathy criteria, anticoagulant therapy (mainly low-molecular-weight heparin) appeared to be associated with decreased mortality.\textsuperscript{104} In an observational study of 2,773 hospitalized COVID-19 patients, systemic anticoagulant therapy was suggested to be associated with improved outcomes, however individualized risk assessments must be made with consideration for bleeding events.\textsuperscript{105}

\textbf{Fulminant Myocarditis}

In some cases, the acute cardiac injury caused by SARS-CoV-2 infection can result in fulminant myocarditis, a rare clinical syndrome with hemodynamic compromise and high mortality rates ranging between 40-70\% (Figure 1).\textsuperscript{106} Fulminant myocarditis is characterized by sudden and diffuse cardiac inflammation, necrosis, and eventual ventricular dysfunction resulting
In cardiogenic shock, malignant arrhythmias, multiorgan failure, and ultimately death.\textsuperscript{107} In the context of COVID-19, several pathophysiological mechanisms have been proposed to justify cardiac inflammation; the systemic exaggerated inflammatory effects caused by COVID-19 (Figure 1), and the hypothesized direct SARS-CoV-2 viral entry via ACE2 receptors in the heart.\textsuperscript{17, 106} While endomyocardial biopsy localized the SARS-CoV-2 virus in a patient with cardiogenic shock, pathological findings demonstrated low-grade myocardial inflammation and absence of cardiomyocyte necrosis.\textsuperscript{16} In some cases, this clinical presentation requires urgent initiation of circulatory support in order to sustain end-organ function, either in the form of inotropic agents or mechanical circulatory support. On the basis of elevated Troponin T levels, mortality was markedly higher in patients with myocardial injury compared to those with normal Troponin T levels (59.6\% vs. 8.9\%, respectively).\textsuperscript{44, 107}

An illustrative case report recently documented that despite normal chest radiographs and minimal respiratory involvement throughout the clinical course, an otherwise healthy 53-year-old COVID-19 patient developed acute perimyocarditis.\textsuperscript{108} This patient was hypotensive, showed diffuse ST elevation on electrocardiography, and had elevated hs-cTnT and NT-proBNP levels. Cardiac magnetic resonance findings showed a circumferential pericardial effusion, severe left ventricular dysfunction (left ventricular ejection fraction of 35\%), and increased wall thickness with diffuse biventricular hypokinesis, all indicative of an acute perimyocarditis. Similar cases have been anecdotally reported, suggesting fulminant myocarditis without overt respiratory manifestations of COVID-19 is possible. Although there are case reports of pericardial effusion and pericarditis in COVID-19 nasopharyngeal swab specimen positive patients,\textsuperscript{109, 110} it is unclear whether the virus has a causal role in this context. In fact, in one case, the serosanguinous pericardial fluid was drained and tested negative for SARS-CoV-2.\textsuperscript{110}
mechanism may possibly be related to a post-cardiac injury syndrome. The diagnosis of fulminant myocarditis should have a high index of suspicion if there is a marked elevation of troponins or there is a new onset of atrioventricular block or QRS prolongation. This is especially relevant in patients that are candidates for mechanical circulatory support.

In COVID-19 patients where hemodynamic shock has already ensued, numerous strategies for reestablishing hemodynamic stability exist including inotropic agents, and mechanical life support such as intra-aortic balloon pumps, Impella devices, and ultimately extracorporeal membrane oxygenation (ECMO). The typical clinical course is a rapidly degenerating COVID-19 patient in respiratory distress, hypotension, and cardiogenic shock, that is then treated with mechanical ventilation and venous-venous or venous-arterial ECMO as a bridge to recovery. Concerns have been raised regarding the limited therapeutic and resource-intensive use of extracorporeal membrane oxygenation (ECMO). Although studies have reported poorer outcomes for COVID-19 patients on ECMO, this is likely due to the severity of the underlying disease which initially predisposes this patient group to an overall lower chance of recovery. Furthermore, the prolonged period of ECMO use, which will likely be necessary in ARDS patients, increases the risks of ECMO-related complications including bleeding, renal, vascular, and infectious injuries. The resource-intensive use of ECMO is also an important consideration as ICUs reach capacity throughout the COVID-19 pandemic. ECMO for 2019 novel Coronavirus Acute Respiratory Disease (ECMOCard) is a prospective multi-center short period incidence observational study currently recruiting patients, that is aiming to describe the clinical features, disease severity, ECMO-related characteristics, complications, and survival of ICU patients with COVID-19.
Regarding the use of primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) in SARS-CoV-2 positive or suspected patients, the recommendation of major cardiovascular societies remains to pursue coronary angiography/primary PCI with aerosol-level personal protective equipment. Adequate infection control is advised due to the increased risks of viral aerosolization during urgent intubation, suctioning, or cardiopulmonary resuscitation, taking into consideration that the vast majority of cardiac catheterization laboratories are not negative-pressure ventilated.

Fibrinolysis has also been controversially suggested as an alternative in relatively stable STEMI cases, in the event that the treating team does not have adequate infectious exposure control or access to rapid nucleic acid testing.

However, in COVID-19 patients presenting with elevated hs-cTn1 or CK-MB and no ST-segment elevations (NSTEMI), a high index of suspicion should be maintained for the possibility of myocarditis. In fact, 10 of 18 COVID-19 patients presenting with ST-segment elevations were diagnosed with noncoronary myocardial injury instead of a myocardial infarction in a recent case-series. Only four of these patients had diffuse ST-segment elevations. Despite focal ST-segment elevations being a shared characteristic among all clinically diagnosed myocardial infarctions, six of the 10 noncoronary myocardial injuries also only had focal ST-segment elevations. While diffuse ST-segment elevations in the absence of reciprocal changes is usually suggestive of a myocarditis, these findings are not ubiquitous. Clinical suspicion for noncoronary myocardial injury should therefore be maintained even if focal ST-segment elevation on electrocardiographic findings of COVID-19 patients present. Despite variability in presentation, the eight patients clinically diagnosed with a myocardial infarction had higher
median peak troponin and D-dimer levels than the noncoronary myocardial injury patients. In an effort to mitigate nosocomial infection risk, noninvasive testing such as computed-tomography coronary angiography or myocardial perfusion imaging tests could be considered for otherwise stable NSTEMI patients. If no underlying CAD is confirmed, these patients should be managed medically, avoiding the risk of aerosol-generating procedures in the cardiac catheterization laboratory. Predetermined resuscitation plans should be organized for patients suspected to develop acute cardiac injury from COVID-19, and careful monitoring of electrocardiographic changes and cardiac and inflammatory biomarkers should guide management throughout hemodynamic recovery.

Cardiovascular care teams will need to develop variable responses based on regional penetrance and healthcare systems capacity in order to balance COVID-19-related and routine cardiovascular care. Telehealth patient consultations and follow-ups are being rapidly adopted in order to triage for urgent care, address symptom control, and monitor medical management of CVD patients. However, care seeking behavior and infection control measures due to the COVID-19 pandemic are expected to substantially disrupt healthcare systems and affect patient time to medical contact. The impact of the COVID-19 pandemic has already been reported to significantly increase time components of STEMI care, resulting in delayed symptom onset to first medical contact, as well as door-to-balloon time.

**Limitations**

While our findings are of significant clinical relevance, several important limitations must be considered. First, while a systematic attempt to summarize the literature was made, our review was not systematic, increasing the possibility of selection and publication biases. Due to the rapidly evolving nature of the COVID-19 pandemic, it would not be feasible to
systematically review the literature as studies containing critical information are being rapidly updated based on government reporting, published in real-time, and not yet indexed in bibliographic databases. Furthermore, data were not quantitatively analyzed due to concerns of overlapping patient populations between reports. Second, our review only included articles published in English language, which introduces an important language bias. The COVID-19 pandemic has affected nearly every country worldwide, resulting in extensive research efforts and data reporting in native languages. Our interpretation of the latest clinical picture is limited to English language reports. Finally, the associations and clinical characteristics identified in this review are only correlative, and await clearly proven causative mechanisms. Important confounders exist in the cross-sectional studies reviewed, including age, medications taken for CVD, and immune strength. In light of the extraordinary and unprecedented time pressure to report such urgent findings, the studies cited in this review were not necessarily operationalized in a systematic or multicenter manner, limiting the overall generalizability of their findings. This is underscored by the in-between study variability in the prevalence rates reported. Larger case-controlled studies that account for these confounding variables will provide necessary insight on the precise risk factors of COVID-19 severity.

CONCLUSION

The COVID-19 pandemic is rapidly evolving, with important cardiovascular considerations. This review synthesizes the cardiovascular implications of COVID-19, and comprehensively addresses large international primary data on the cardiovascular epidemiology and treatment considerations of COVID-19. Hypertension, diabetes, and CVD are the most common comorbidities in COVID-19 patients, and these factors have been associated with the progression and severity of COVID-19. However, elder populations, whom develop more severe
COVID-19 complications, are naturally exposed to these comorbidities, underscoring the possible confounding of age. Observational data supports international cardiovascular societies recommendation to not discontinue ACEi/ARB therapy in patients with guideline indications out of fear for the increased risk of SARS-CoV-2 infection, severe disease, or death. In addition to the cardiotoxicity of experimental antivirals and potential interactions of experimental therapies with cardiovascular drugs, several strategies for cardiovascular protection have been recommended in COVID-19 patients with underlying CVD. Troponin elevation is associated with increased risk of in-hospital mortality and adverse outcomes in patients with COVID-19. Cardiovascular care teams should have a high index of suspicion for fulminant myocarditis-like presentations being SARS-CoV-2 positive, and remain vigilant for cardiovascular complications in COVID-19 patients.
REFERENCES


58. Yuan S. Statins May Decrease the Fatality Rate of Middle East Respiratory Syndrome Infection. *mBio.* 2015;6:e01120.


FIGURE LEGENDS

Figure 1. Hypothesized pathophysiological mechanisms of the systemic and cardiovascular interactions of the SARS-CoV-2 virus and ACE2.

Abbreviations: ACE2=Angiotensin-Converting Enzyme 2; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2.
Table 1: Cardiovascular Clinical Presentations of COVID-19 Patients in Identified Observational Studies in China*  

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (n)</th>
<th>Location</th>
<th>Median Age</th>
<th>Smoking †, n (%)</th>
<th>Hypertension, n (%)</th>
<th>Diabetes, n (%)</th>
<th>CVD, n (%)</th>
<th>CAD, n (%)</th>
<th>Cerebrovascular Disease, n (%)</th>
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<td>Guan et al. (2020)</td>
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</table>

† Abbreviations: CAD=Coronary Artery Disease; COVID-19=Coronavirus Disease 2019; CVD=Cardiovascular Disease.  
‡ Current or former smoker.  
§ Data reported as mean.  
§§ This study pooled cardiovascular and cerebrovascular diseases when reporting baseline characteristics.  
|| This case-series was of fatal COVID-19 patients.
### Table 2. Cardiovascular Clinical Presentations of Hospitalized, Critically Ill, or Fatal COVID-19 Cases in Identified Observational Studies Primarily Outside of China

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size (n)</th>
<th>Location</th>
<th>Median Age</th>
<th>Hypertension, n (%)</th>
<th>Diabetes, n (%)</th>
<th>CVD, n (%)</th>
<th>CAD, n (%)</th>
<th>Atrial Fibrillation, n (%)</th>
<th>Congestive Heart Failure, n (%)</th>
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</thead>
<tbody>
<tr>
<td>Richardson et al. (2020)†</td>
<td>5,700</td>
<td>New York City Area, USA</td>
<td>63.0</td>
<td>3026 (56.6)</td>
<td>1808 (33.8)</td>
<td>-</td>
<td>595 (11.1)</td>
<td>-</td>
<td>371 (6.9)</td>
</tr>
<tr>
<td>COVID-19 Surveillance Group* (2020)†</td>
<td>2,848</td>
<td>Italy</td>
<td>81</td>
<td>1,940 (68.1)</td>
<td>870 (30.5)</td>
<td>-</td>
<td>804 (28.2)</td>
<td>642 (22.5)</td>
<td>457 (16.0)</td>
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<tr>
<td>Grasselli et al. (2020)</td>
<td>1,591</td>
<td>Lombardy region, Italy</td>
<td>63</td>
<td>509 (49.0)</td>
<td>180 (17.0)</td>
<td>223 (21.0)</td>
<td>-</td>
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<tr>
<td>Goyal et al. (2020)</td>
<td>393</td>
<td>New York City, USA</td>
<td>62</td>
<td>197 (50.1)</td>
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<td>-</td>
<td>54 (13.7)</td>
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<td>28 (7.1)</td>
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<tr>
<td>Myers et al. (2020)</td>
<td>377</td>
<td>Northern California, USA</td>
<td>61</td>
<td>164 (43.5)</td>
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<tr>
<td>Onder et al. (2020)</td>
<td>355</td>
<td>Italy</td>
<td>79†</td>
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<td>Arentz et al. (2020)</td>
<td>21</td>
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<td>9 (42.9)</td>
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</table>

* Abbreviations: CAD=Coronary Artery Disease; COVID-19=Coronavirus Disease 2019; CVD=Cardiovascular Disease; USA=United States of America.
† These case-series were of hospitalized COVID-19 patients.
‡ These case-series were of severe or fatal COVID-19 patients.
§ CVD includes cardiomyopathy and heart failure.
|| Data reported as mean.
### Table 3. Cardiovascular Society Recommendations on RAAS Antagonists in the COVID-19 Patient

<table>
<thead>
<tr>
<th>Society</th>
<th>Date of Recommendation</th>
<th>RAAS Antagonists Recommendation</th>
</tr>
</thead>
</table>
| AHA/HFSA/ACC                                 | March 17, 2020         | • Continuation of ACEis/ARBs in COVID-19 patients with pre-existing indications (heart failure, hypertension, CAD).  
• Careful consideration prior to addition/removal of any CVD treatments in COVID-19 patients. |
| Canadian Cardiovascular Society              | March 20, 2020         | • Continuation of ACEi/ARB/ARNi unless clinically contraindicated (symptomatic hypotension, shock, AKI, hyperkalemia). |
| European Society of Hypertension            | April 15, 2020         | • Stable COVID-19 patients should continue ACEi/ARB treatment according to 2018 ESC/ESH guidelines.  
• Assess COVID-19 patients with severe symptoms, sepsis, or hemodynamic instability on a case-by-case basis for the discontinuation of blood pressure lowering drugs, with consideration for current guidelines. |
| Hypertension Canada                          | March 13, 2020         | • Continue anti-hypertensive treatment.                                                          |
| International Society of Hypertension       | March 16, 2020         | • Routine use of ACEis/ARBs in hypertensive patients despite COVID-19 concerns.                  |

Abbreviations: ACC=American College of Cardiology; ACEi=Angiotensin-Converting Enzyme inhibitor;  
ARB=Angiotensin Receptor Blocker; AHA=American Heart Association; AKI=Acute Kidney Injury;  
ARNi=Angiotensin Receptor-Neprilysin Inhibitor; CAD=Coronary Artery Disease; COVID-19=Coronavirus  
Disease 2019; ESC=European Society of Cardiology; HFSA=Heart Failure Society of America; RAAS=Renin-Angiotensin-Aldosterone System.
Table 4. Summary of Current COVID-19 Experimental Therapies and Adverse Cardiovascular Drug Interactions*

<table>
<thead>
<tr>
<th>Experimental Therapy</th>
<th>Antiarrhythmic Agents</th>
<th>Anti-coagulant, Anti-platelet, Fibrinolytic Agents</th>
<th>Beta Blockers</th>
<th>Calcium Channel Blockers</th>
<th>Hypertension/Heart Failure Agents</th>
<th>Inotropes and Vasopressors</th>
<th>Lipid Lowering Agents</th>
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<tbody>
<tr>
<td><strong>Atazanavir</strong></td>
<td>Amiodarone</td>
<td>Apixaban, Clopidogrel, Dabigatran</td>
<td>Potential Interaction</td>
<td>Potential Interaction</td>
<td>Aliskiren, Eplerenone, Ivabradine</td>
<td>NC</td>
<td>Lovastatin, Simvastatin</td>
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<td>Bepridil</td>
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</tbody>
</table>

* Abbreviations: COVID-19=Coronavirus Disease 2019; NC=No Clinically significant interaction.

† All information was adapted from the Liverpool Drug Interactions Group (updated on July 13, 2020). Only drugs with strong recommendations against being coadministered were listed, however classes with listed drugs could also have potential interactions. “Potential interaction” was used to report drug classes where at least one drug interaction was expected to require a dose adjustment or additional monitoring. Potential interactions of weak intensity were considered similar to NC. For complete information, visit: Detailed recommendations for interactions with experimental COVID-19 antiviral therapies, 13 July 2020, University of Liverpool, available from www.covid19-druginteractions.org, accessed 21 July 2020.