Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic

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Myocardial injury, myocarditis, and acute coronary syndromes

Myocardial injury, as defined by an increased troponin level, can occur due to myocardial ischemia or non-ischemic myocardial processes including myocarditis (6,42,43). With severe respiratory infection and hypoxia, especially in the setting of severe infection and ARDS due to COVID-19, it is likely that a number of patients will develop such injury. Elevated serum troponin levels have been described in many patients infected with COVID-19, with significant differences noted between patients who died and those who survived to discharge (21,44). In a meta-analysis of 4 studies including a total of 341 patients, standardized mean difference of cardiac troponin I levels were significantly higher in those with severe COVID-19 related illness compared to those with non-severe disease (25.6, 95% CI 6.8-44.5) (45). Reports have also suggested that acute cardiac injury – which includes not only elevation of cardiac biomarkers to > 99th percentile of the upper reference limit, but also electrocardiographic and echocardiographic abnormalities – is highly prevalent in patients with COVID-19 and is associated with more severe disease and worse prognosis. Cohort studies from hospitalized patients in China estimate that such injury occurs in 7-17% of hospitalized patients with the disease (1,6,19) and is significantly more common in patients admitted to the ICU (22.2% vs. 2.0%, $p<0.001$) and among those who died (59% vs. 1%, $p<0.0001$) (6,8). However, troponin levels can be exacerbated in patients with renal insufficiency due to delayed excretion, which is common in patients with advanced disease. Given limited high-quality data, and the heterogeneity of definitions across the studies, standardized data collection methods are recommended using the most recent Universal Definition of Myocardial Infarction (MI) (43). Prior studies in other coronavirus species (MERS-CoV) have demonstrated evidence of acute myocarditis using cardiac magnetic resonance imaging (46), and myocardial inflammation and damage have been reported with COVID-19 infection. Among 68 deaths in a case series of 150 patients with COVID-19, 7% were attributed to myocarditis with circulatory failure and in 33% of cases which myocarditis may have played a contributing role to the patient's demise (21). Other reports have described fulminant myocarditis in the setting of high viral load with autopsy findings of inflammatory mononuclear infiltrate in myocardial tissue (26,47,48). Pericardial involvement has not yet been reported but further study is needed. In addition, the extent to which supply and demand mismatch (Type 2 MI) in patients with underlying CVD have contributed to the CV manifestations of the syndrome is uncertain. Case reports of acute coronary syndromes (ACS) (Type 1 MI) in the setting of COVID-19 have yet to be published. Nonetheless, the profound inflammatory response and hemodynamic changes associated with severe disease may confer risk for atherosclerotic plaque rupture in susceptible patients (6). In this regard, analysis by Kwong and colleagues demonstrated that patients with acute respiratory infections are at elevated risk for subsequently developing acute myocardial infarction after influenza (incidence ratio [IR] 6.1, 95% CI 3.9-9.5) and after non-influenza viral illnesses including other coronavirus species (IR 2.8, 95% CI 1.2–6.2) (36). The development of care pathways and protocols for COVID-19 patients with STEMI suggest that both within and outside of China such a clinical scenario is highly probable (49). Additionally, it is important to note potential overlapping symptomatology between ACS and COVID-19. While the predominant presenting symptoms of COVID-19 are respiratory, a case report described a patient in Italy with chest pain and electrocardiographic changes for which the cardiac catheterization lab was activated. Notably, the patient was found to be free of obstructive coronary artery disease but ultimately tested positive for COVID-19 (50). Moving forward as the virus continues to infect patients with significant CV risk factors, or established CVD, cases of ACS in the setting of COVID-19 are likely to develop. The true

prevalence in this setting may be underreported given the logistical challenges associated with limited testing and cardiac catheterization laboratory availability in the setting of this outbreak. For further recommendations for the care and management of COVID-19 patients in the cardiac catheterization laboratory, please see the joint American College of Cardiology (ACC) and Society of Cardiovascular Angiography and Intervention (SCAI) guidance statement (51).

Cardiac Arrhythmia and Cardiac Arrest.

Cardiac arrhythmias are another common CV manifestation described in patients with COVID-19 infection. While nonspecific, heart palpitations were part of the presenting symptomology in 7.3% of patients in a cohort of 137 patients admitted for COVID-19 disease (26). In hospitalized COVID-19 patients, cardiac arrhythmia was noted in 16.7% of 138 patients in a Chinese cohort and was more common in ICU patients compared to non-ICU patients (44.4% vs. 6.9%) (19). Unfortunately, specifics about the types of arrhythmias that occur in these patients are yet to be published or presented. High prevalence of arrhythmia might be, in part, attributable to metabolic disarray, hypoxia, neurohormonal or inflammatory stress in the setting of viral infection in patients with or without prior CVD. However, new onset of malignant tachyarrhythmias in the setting of troponin elevation should raise suspicion for underlying myocarditis (44,52).

Cardiomyopathy and heart failure.

Zhou and colleagues reported that heart failure was observed in 23.0% of patients with COVID-19 presentations (6). Notably, heart failure was more commonly observed than acute kidney injury in this cohort and was more common in patients who did not survive the hospitalization compared to those who did survive (51.9% vs. 11.7%). Whether heart failure is most commonly due to exacerbation of pre-existing left ventricular dysfunction versus new cardiomyopathy (either due to myocarditis or stress cardiomyopathy) remains unclear (53). Right heart failure and associated pulmonary hypertension should be also considered, in particular in the context of severe parenchymal lung disease and ARDS.

Cardiogenic and mixed shock. The predominant clinical presentation of COVID-19 is acute respiratory illness, which may lead to ARDS manifested as ground-glass opacities on chest imaging (54) and hypoxemia. However, similar features may be seen in the case of *de novo* or coexisting cardiogenic pulmonary edema. As such, it is important consider cardiogenic or mixed cardiac plus primary pulmonary causes of respiratory manifestations in COVID-19. Historically, right heart catherization was used to determine pulmonary capillary wedge pressure in order to aid in this distinction, although this has been removed from the Berlin criteria used for the diagnosis of ARDS. Rather, the Berlin criteria utilize timing of symptom onset, imaging with bilateral pulmonary opacities, and lack of volume overload to identify patients with ARDS (55). In many cases, serum brain natriuretic peptide (BNP) and echocardiography can help clarify the diagnosis (56,57). However, if these tests are unclear and there remains concern for mixed presentation, pulmonary artery catheterization should be considered in select cases to assess filling pressures, cardiac output, and to guide clinical decision-making, given the different management approaches for ARDS and cardiogenic shock. Finally, it is crucial to determine whether or not a concomitant cardiogenic component is present when considering mechanical respiratory and circulatory support with extracorporeal membranous oxygenation (ECMO) or other techniques, as this may lend to changes in device selection (e.g. venovenous vs. venoarterial ECMO cannulation). Regardless, in the most severe of infections with ARDS and necrotizing pneumonias, patient prognosis may be poor even with ECMO support. In a case series of 52 critically ill patients with COVID-19, 83.3% (5/6) of patients who were treated with ECMO did not survive. Further studies regarding the utility of ECMO support in advanced COVID-19, including which patients may (or may not) benefit and whether concomitant left ventricular venting should be done, are warranted (58).

Venous thromboembolic disease.

COVID-19 infected patients are likely at increased risk venous of thromboembolism (VTE). Though there are no published case series thus far, there are reports of abnormal coagulation parameters in hospitalized patients with severe COVID-19 disease (59,60). In a multicenter retrospective cohort

study from China, elevated D-dimer levels (>1g/L) were strongly associated with in-hospital death, even after multivariable adjustment (OR 18.4 95% CI 2.6-128.6, p=0.003) (6). In another study comparing COVID-19 survivors to non-survivors, non-survivors had significantly higher D-dimer and fibrin degradation products (FDP) levels and 71.4% of non-survivors met clinical criteria for disseminated intravascular coagulation (DIC) during the course of their disease (59). In addition to DIC, critically ill patients with prolonged immobilization are inherently at high risk for VTE. Vascular inflammation may also contribute to the hypercoagulable state and endothelial dysfunction in such patients. In the setting of critically ill COVID-19 patients who demonstrate clinical deterioration as evidenced by hypoxia or hemodynamic instability, thromboembolic disease should be considered. The optimal thromboprophylactic regimen for patients hospitalized with COVID-19 related illness is not known. As such, contemporary guideline endorsed strategies should be observed (61). Given the drug-drug interactions between some antiviral treatments and direct oral anticoagulants, low molecular weight heparins, or unfractionated heparin with or without mechanical prophylaxis are likely to be preferred in acutely ill hospitalized patients.

Drug Therapy and COVID-19: Interactions and Cardiovascular Implications

Data regarding antiviral therapies and other treatment strategies, as well as their potential interaction with CV medications and CV toxicities are summarized in Tables 3-5. Although currently there are no specific effective therapies for COVID-19, various pharmacologic agents are under activeinvestigation. As these drugs are being studied, it is important to review the potential CV side effects and interactions with other CV medications.

Antiviral Therapy: Antivirals are at the forefront of medications under study for the treatment COVID-19 and the clinical trial identifiers for each are listed in Table 3. Ribavirin and remdesivir are two such agents that bind to the active site on the RNA-dependent RNA polymerase on SARS-CoV2 (62), while lopinavir/ritonavir inhibits replication of RNA virus and has evidence of a synergistic effect *in vitro* with ribavirin (63). Ribavirin and lopinavir/ritonavir are under investigation in clinical trials for COVID-19 and have been used for years as components of treatment for hepatitis C and HIV, respectively (64,65). While ribavirin has no characterized direct CV toxicity, lopinavir/ritonavir may result in QT and PR interval prolongation, especially in patients who have a baseline abnormality (long QT) or those who are at risk for conduction abnormalities including those taking other QT prolonging drugs (65).

Anticoagulant drugs: Both ribavirin and lopinavir/ritonavir have the potential to affect anticoagulant dosing: ribavirin has variable effects on warfarin dosing (66) and lopinavir/ritonavir may require dose reductions or avoidance of CYP3A mediated drugs such as rivaroxaban and apixaban (67,68).

P2Y12 inhibitors: Lopinavir/ritonavir can also influence the activity of P2Y12 inhibitors through CYP3A4 inhibition, which results in decreased serum concentrations of the active metabolites of clopidogrel and prasugrel and increased serum concentrations of ticagrelor. Given the increase in serum ticagrelor levels with such medications (69,70), concomitant use with ticagrelor is discouraged in the United States and Canada due to excess in bleeding risk. Conversely, there is evidence that clopidogrel may not always provide sufficient platelet inhibition in the setting of concomitant administration of lopinavir/ritonavir, whereas this was not the case with prasugrel as assessed by the VerifyNow P2Y12 assay (71,72). If P2Y12 inhibition is needed during treatment with lopinavir/ritonavir, prasugrel can be used; however, if contraindicated (i.e. history of stroke or TIA, low body mass index, or active pathological bleeding), a testing-guided approach (e.g. with P2Y12 platelet function assays) may be considered with alternate antiplatelet agents. Details about switching between P2Y12 inhibitors have been described elsewhere (73). Finally, metabolism of the intravenous P2Y12 inhibitor, cangrelor, is independent of hepatic function, therefore a drug interaction is not expected (74).

Statins: HMG-CoA reductase inhibitors also have the potential to interact with the combination of lopinavir/ritonavir and can result in myopathy due to elevated statin levels when administered together. Lovastatin and simvastatin, in particular, are contraindicated for co-administration with lopinavir/ritonavir due to risk of rhabdomyolysis. Other statins, including atorvastatin and

rosuvastatin, should be administered at the lowest possible dose but not to exceed the maximum dose stated in the package insert while on lopinavir/ritonavir (65). Remdesivir is an investigational drug previously evaluated in the Ebola epidemic and is now being studied in patients with COVID-19. The drug is currently available in clinical trials and through compassionate use from Gilead Sciences, Inc (Foster City, California). While extensive CV toxicities and medication interactions have yet to be reported, prior evaluation of this drug during the Ebola outbreak did note the development of hypotension and subsequent cardiac arrest after loading dose in one patient (among 175 total) (75).

ACE2 and potential therapeutic implications: As the ACE2 receptor is the mechanism of entry for SARS-CoV2, some data suggest that ACE inhibitors (ACEi) and angiotensin receptor blockers (ARB) may upregulate ACE2, thereby increasing susceptibility to the virus (Figure 1) (5). In contrast other studies show that ACEi/ARB may potentiate the lung protective function of ACE2, which is an angiotensin II inhibitor (80-82). Thus, the therapeutic implications for ACEi/ARB therapy during COVID-19 infection is unclear. Overall, there is insufficient data to suggest any mechanistic connections between ACEi/ARB therapy with contracting COVID-19 or with severity illness once infected.