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Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease

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Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic impacting nearly 170 countries/regions and more than 285,000 patients worldwide. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which invades cells through the angiotensin converting enzyme 2 (ACE2) receptor. Among those with COVID-19, there is a higher prevalence of cardiovascular disease and more than 7% of patients suffer myocardial injury from the infection (22% of the critically ill). Despite ACE2 serving as the portal for infection, the role of ACE inhibitors or angiotensin receptor blockers requires further investigation. COVID-19 poses a challenge for heart transplantation, impacting donor selection, immunosuppression, and post-transplant management. Thankfully there are a number of promising therapies under active investigation to both treat and prevent COVID-19.

Key Words: COVID-19; myocardial injury; pandemic; heart transplant

Coronavirus disease 2019 (COVID-19) is a global pandemic. As of March 21st, 2020 infected patients were present in 167 countries/regions around the world and there were more than 285,000 cases worldwide with nearly 12,000 fatalities.[1] While the outbreak began in China, the number of cases outside of China exceeded those in China on March 15th, 2020 and are currently rising at an exponential rate. Furthermore, the number of fatalities in Italy now exceeds the total in China. COVID-19 interacts with cardiovascular system on multiple levels, increasing morbidity in patients with underlying cardiovascular conditions and provoking myocardial injury and dysfunction.

COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This novel single-stranded enveloped RNA virus is the seventh known human coronavirus. SARS-CoV-2 is unlike the other coronaviruses known to cause the common cold (229E, OC43, NL63, and HKU1), but similar to the zoonotic severe acute respiratory syndrome coronavirus (SARS-CoV) from 2002 (SARS)[2] and the Middle East respiratory syndrome coronavirus (MERS-CoV) from 2012 (MERS).[3] SARS-CoV-2 is believed to have originated in bats, similar to many other coronaviruses, as it shares 89-96% nucleotide identity with bat coronaviruses.[4] Like SARS and MERS, it is believed SARS-CoV-2 moved from bats to an intermediate host (possibly a Malayan Pangolin, which shares 91% nucleotide identity) and then to humans.[5] (Figure 1)

SARS-CoV-2 infection is caused by binding of the viral surface spike protein to the human angiotensin-converting enzyme 2 (ACE2) receptor following activation of the spike protein by transmembrane protease serine 2 (TMPRSS2).[6] ACE2 is expressed in the lung (principally Type II alveolar cells[7]) and appears to be the predominant portal of entry. ACE2 is highly expressed in the heart as well, counteracting the effects of angiotensin II in states with

excessive activation of the renin-angiotensin system such as hypertension (HTN), congestive heart failure (CHF), and atherosclerosis.[8] In addition to the heart and lung, ACE2 is expressed in the intestinal epithelium, vascular endothelium, and the kidneys, providing a mechanism for the multi-organ dysfunction that can be seen with SARS-CoV-2 infection.[8, 9] There is increasing evidence linking COVID-19 with increased morbidity and mortality from cardiovascular disease. In this review, we will summarize the rapidly evolving data in this field.

Clinical Presentation

SARS-CoV-2 is spread predominantly via respiratory droplets, but also can be aerosolized or detected in the stool. Transmission may occur from both symptomatic and asymptomatic patients, with secondary infection rates ranging 0.5-5%.[10, 11] SARS-CoV-2 has been demonstrated to remain stable for up to 3 hours in the aerosolized form, up to 24 hours on cardboard, and as many as three days on plastic or stainless steel.[12] The median incubation time is 4-5 days and 97.5% will experience symptoms within 11.5 days of exposure.[13, 14]

Early reports suggest the most common symptoms are fever (88%) and dry cough (67.7%), which are shared with many other viral syndromes (Figure 2). Conspicuously, rhinorrhea (4.8%) and gastrointestinal symptoms (diarrhea 4-14%, nausea/emesis 5%) appear to be less frequent with COVID-19.[11] Reports from China demonstrate that a significant majority of patients (81%) had mild symptoms (no pneumonia or mild pneumonia) from COVID-19. Among those with more significant symptoms, 14% experienced severe symptoms (dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours) and 5% were critical (respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[9]

The case fatality rate (CFR, number of deaths/number of those diagnosed) has differed significantly around the world. The original reports from China suggested a CFR of 2.3%[15] with subsequent reports estimating the symptomatic case fatality risk (the probability of dying after developing symptoms) was lower at 1.4%[16], which contrasts with influenza (0.1%), MERS (34%), and SARS (10%).[17] Based on reported data from March 21st, 2020, the CFR varies significantly by country**:** China 4.0% (81,304 cases), Italy 8.6% (47,021 cases), Iran 7.5% (20,610 cases), Spain 5.4% (25,374 cases), South Korea 1.2% (8,779 cases), Germany 0.3% (21,828 cases), and the United States 1.3% (22,043 cases).[1] The CFR rises rapidly with increasing age; the CFR is less than 1% for those under 50 years of age, rising to 1.3% for 50 year olds, 3.6% for 60 year olds, 8% for septuagenarians, and 14.8% for octogenarians.[15] Similarly, the CFR increases with disease severity, as there were no deaths reported among the mild or severe cases in the Chinese cohort; however, the CFR was 49% among critical patients. Furthermore, compared to patients with no comorbidities in whom the CFR is 0.9%, patients with medical comorbidities have a significantly increased CFR: 10.5% for cardiovascular disease (CVD); 7.3% for diabetes mellitus (DM); 6.3% for COPD; 6% for HTN; and 5.6% for cancer.[15]

COVID-19 in Patients with Cardiovascular Disease

Cardiovascular disease was a common comorbidity in patients with COVID-19 predecessors SARS and MERS. In SARS, the prevalence of DM and CVD was 11% and 8% respectively, and the presence of either comorbidity increased the risk of death twelvefold.[2, 18] DM and HTN were prevalent in about 50% of cases of MERS, while CVD was present in approximately 30% of patients.[19] The increased presence of cardiovascular comorbidities holds true for COVID-19 as well, most notably among those with more severe disease. In one cohort of 191 patients from Wuhan, China, any comorbidity was present in 48% (67% of non-survivors), HTN was present

in 30% (48% of non-survivors), DM in 19% (31% of non-survivors), and CVD in 8% (13% of non-survivors).[20] In a cohort of 138 hospitalized patients with COVID-19, comorbidities were similarly prevalent (46% overall, 72% in patients requiring an ICU), as were cardiovascular comorbidities: HTN in 31% (58% in patients requiring an ICU), CVD in 15% (25% in patients requiring an ICU), and DM in 10% (22% in patients requiring an ICU).[21] Analysis of an outpatient and inpatient cohort of 1,099 patients with COVID-19 reported that 24% had any comorbidity (58% among those with intubation or death), with 15% having HTN (36% among those with intubation or death), 7.4% with DM (27% among those with intubation or death), and 2.5% with coronary heart disease (9% among those with intubation or death).[13] Data from the National Health Commission (NHC) of China demonstrated that 35% of patients diagnosed with COVID-19 had HTN and 17% had coronary heart disease.[22] Lastly, a recent meta-analysis of eight studies from China including 46,248 infected patients showed the most prevalent comorbidities were HTN (17±7%, 95% CI 14-22%) and DM (8±6%, 95% CI 6-11%), followed by cardiovascular diseases (5±4%, 95% CI 4-7%).[23] The mechanism of these associations remains unclear at this time. Potential explanations include CVD being more prevalent in those with advancing age, a functionally impaired immune system, elevated levels of ACE2, or a predisposition to COVID-19 for those with CVD.

COVID-19 and Myocardial Injury

Myocardial injury, evidenced by elevated cardiac biomarkers, was recognized among early cases in China. In the aforementioned study of 138 hospitalized patients with COVID-19 in Wuhan China, cardiac injury (elevated high sensitivity Troponin I [hs-cTnI] or new ECG or echocardiographic abnormalities) was present in 7.2% of patients overall, and 22% that required ICU care.[21] The report from the NHC of China reported that almost 12% of patients without

known CVD had elevated troponin levels or cardiac arrest during the hospitalization.[22] Notably, hs-cTnI was above the 99th percentile upper reference limit in 46% of non-survivors as opposed to 1% of survivors.[20] (Figure 3)

Early reports indicate that there are two patterns of myocardial injury with COVID-19. One study demonstrated that at 4 days following symptom onset, median hs-cTnI levels were 8.8 pg/mL in non-survivors vs. 2.5 pg/mL in survivors. During follow-up, the median hs-cTnI among survivors did not change significantly (2.5-4.4 pg/mL), whereas it rose to 24.7 pg/mL on Day 7, to 55.7 pg/mL on Day 13, to 134.5 pg/mL on Day 19, and to 290.6 pg/mL on Day 22 for non-survivors.[20] Notably, the median time to death from the onset of symptoms was 18.5 days (IQR 15 – 20 days). The rise in hs-cTnI tracks with other inflammatory biomarkers (D-dimer, ferritin, interleukin-6 (IL-6), lactate dehydrogenase), raising the possibility that this reflects cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury. In contrast, reports of patients presenting with predominantly cardiac symptoms suggest a different pattern, potentially viral myocarditis or stress cardiomyopathy. For example, one case recently published involved a man presenting with chest pain and ST-segment elevation on his electrocardiogram, but without coronary obstruction. An echocardiogram noted left ventricular dysfunction (ejection fraction 27%, LVEDD 5.8cm) and elevated cardiac biomarkers (troponin T >10 ng/mL, NT-proBNP>21,000 pg/mL).[24] Following a therapeutic approach which included intravenous immunoglobulin and steroids, ejection fraction and cardiac biomarkers normalized within three weeks. In another report from China, a 63 year old man with no past cardiac history presented with both severe respiratory manifestation and evidence of fulminant myocarditis with an enlarged left ventricle (LVEDD 6.1 cm) and depressed left ventricular function (ejection fraction 32%). The patient had an elevated troponin-I (>11 ng/mL) and NT-proBNP (>22,000

pg/ml). Given the severity of his cardiogenic shock, he was placed on extracorporeal membrane oxygenation and was treated with intravenous immunoglobulin, steroids, anti-viral therapy and renal replacement therapy. The patient ultimately showed recovery of his ventricular function within 2 weeks.[25] While both of these patients were treated with glucocorticoids it is unclear the impact of this therapy, as both the WHO and CDC currently do not recommend glucocorticoid use unless otherwise indicated (e.g. chronic obstructive pulmonary disease or asthma exacerbation).[26, 27] Similarly a report from the NHC of China comments that a subset of patients presented with palpitations and chest pain, not the typical fever and cough.[22] Based on available but limited data, it appears that the incidence of fulminant myocarditis and profound cardiogenic shock is low; however, the rate of recovery and mode of treatment are yet to be determined.

The exact mechanism of cardiac involvement in COVID-19 remains under investigation. One potential mechanism is direct myocardial involvement mediated via ACE2. A murine model demonstrated pulmonary infection with SARS-CoV also precipitated an ACE2-dependent myocardial infection.[28] Among humans, during the Toronto SARS outbreak, SARS-CoV viral RNA was detected in 35% of autopsied hearts.[29] Other suggested mechanisms of COVID-19 related cardiac involvement include a cytokine storm, mediated by an imbalanced response among subtypes of T helper cells[20], and hypoxia induced excessive intracellular calcium leading to cardiac myocyte apoptosis.[22]

Role of angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB)

ACE2 is a homolog of ACE that converts angiotensin II to angiotensin 1-7, thereby diminishing vasoconstriction mediated by the renin angiotensin system. The use of ACEi and ARB are common in cardiovascular disorders (HTN, coronary artery disease, congestive heart failure, and

DM). There are conflicting data from studies demonstrating whether these drugs increase[30-32] or have minimal effect on ACE2 levels[33-36]. SARS-CoV-2 entry into cells is ACE2 dependent (Figure 4); however, ACE2 appears to be protective against acute lung injury. In a murine model, binding of the SARS-CoV spike protein to ACE2 caused ACE2 downregulation, leading to an increase in angiotensin II and ultimately increased pulmonary vascular permeability, inducing pulmonary edema, and reduced lung function. However, treatment with recombinant ACE2[37] and losartan[38] mitigated the degree of lung injury. On this basis losartan is being studied for potential mitigation of lung injury among both inpatients and outpatients with COVID-19.[39, 40] At this time nearly all major societies have recommended against adding or stopping ACEi, ARB, or other RAAS antagonists in this setting, unless done on clinical grounds independently of COVID-19, given the lack of evidence currently available on their potential benefit or harm.

Heart Transplantation in the Era of COVID-19

During prior coronavirus epidemics (SARS & MERS), transplant patients presented with similar symptoms as the general population.[41, 42] In the current pandemic, a case study described the clinical courses of two heart transplant recipients from the Hubei province of China. Both patients presented with fevers and had laboratory and CT scans that were similar to non-immunosuppressed individuals with bilateral ground glass opacities in a peripheral distribution. One had relatively mild disease, while the other required hospitalization requiring supplemental oxygen.[43] Both survived and were treated with antibiotics and antivirals, while the more ill patient also required cessation of immunosuppression, along with treatment with methylprednisolone and IVIG. A survey of 87 heart transplant recipients in Wuhan, China did not find a higher risk of infection with SARS-CoV-2 if routine preventive measures were used, and while encouraging, this needs to be confirmed in larger populations.[44] Further, we do not

know if transplant patients will experience differences in disease severity or duration compared with the non-immunosuppressed population.

The ongoing pandemic has raised the question of whether to continue offering heart transplantation due to concerns about a risk for exposure to COVID-19 during hospitalization, as well as challenges in controlling the infection in the context of high levels of immunosuppression. Current recommendations are to continue heart transplantation without changes in immunosuppression provided the recipient has not tested positive for SARS-CoV-2 and has not had exposure to or symptoms of COVID-19 in the prior two to four weeks.[45, 46] Major societal recommendations include avoiding donors with known or suspected COVID-19 and if a donor had COVID-19, they should be COVID-19 free (by PCR) for at least 14 days (owing to the incubation period of ~5 days and onset of symptoms in ~11.5 days).[14, 47] We recognize the difficulties of this decision with increasing prevalence of COVID-19 in the donor population, that may be asymptomatic, especially if the donor cannot be tested for COVID-19. Recommended management of transplant recipients who developed COVID-19, based on very limited data to date, is supportive care and continuation of immunosuppression for mild COVID-19 with reduction of the anti-metabolite (mycophenolate or azathioprine) and further treatment based on disease severity and drug availability.[45] Notably, one potential treatment option for COVID-19 are protease inhibitors, which will increase calcineurin inhibitor levels.

Treatment

Preventive measures are the best strategy for COVID-19 at this time. While vaccines and monoclonal antibodies against SARS-CoV-2 are in development, a number of other investigational therapies, using repurposed clinically approved drugs targeting SARS-CoV-2 cell invasion and replication, may be considered. Recombinant human ACE2 (APN01) was

developed in 2010 and could potentially both neutralize the virus and protect against acute lung injury. It has been demonstrated to be safe and reduce levels of both angiotensin II and IL-6 in a Phase II study of acute respiratory distress syndrome[48]. It is currently under investigation in China in severe COVID-19. The serine protease inhibitor camostat mesylate, which is approved in Japan for chronic pancreatitis and postoperative reflux esophagitis among other indications, has been shown to block TMPRSS2 activity and inhibit SARS-CoV entry into cells.[49] This well tolerated therapy has been proposed as a treatment to prevent SARS-CoV-2 spike protein activation, thereby preventing cell entry and controlling infection. Remdesevir is a broad spectrum antiviral that interrupts RNA replication by acting as an nucleotide analog.[50] Initially developed to treat Ebola, it has been demonstrated to have both *in vitro* activity against SARS-CoV-2 and prevent and reduce disease severity in MERS-CoV in primates.[51, 52] It has been safe in prior trials and currently is enrolling in clinical trials in China[53, 54] and the United States.[55, 56] Chloroquine (anti-malarial drug) and hydroxychloroquine (rheumatoid arthritis or systemic lupus erythematosus treatment) block SARS-CoV-2 cell entry *in vitro* at similar concentrations that are achieved with treatment for rheumatoid arthritis (500 mg twice daily for chloroquine & 600 mg twice a day loading followed by 400-600 mg a day for hydroxychloroquine) and trials with these agents are ongoing.[52, 57-60] Additionally, early studies suggest clinical benefit in COVID-19 with reduction in pneumonia severity, decreased length of hospitalization, and earlier viral clearance.[61] The combination protease inhibitor lopinavir/ritonavir used in HIV was demonstrated to have *in vitro* activity against SARS-CoV and improved clinical outcomes when used in combination with ribavirin for SARS.[62] There have been reports of its success in treating SARS-CoV-2, though the first randomized control trial did not demonstrate statistically significant benefit among hospitalized patients with COVID-19.[63] In this study of 199 patients,

28 day mortality was 5.8% lower (95% CI -17.3-5.7%) for the lopinavir/ritonavir treated patients and the median time to improvement was 1 day shorter; further data are needed to determine the role of lopinavir/ritonavir. Antiviral medications typically used for influenza (oseltamivir and arbidol) have been applied, without clinical efficacy data available. Another drug approved for influenza, favipiravir, is considered promising as it inhibits RNA polymerase and is being studied in a clinical trial in China.[64] Other proposed strategies include interferon and convalescent serum.

Tocilizumab and sarilumab are IL-6 receptor antagonists used in the treatment of rheumatoid arthritis, while tocilizumab also has the indication for the treatment of cytokine release syndrome as is seen with chimeric antigen receptor-T cell (CAR-T) therapy. These may be potential therapies for COVID-19 patients that display elements of cytokine storm or secondary hemophagocytic lymphohistiocytosis with markedly elevated IL-6, ferritin, D-dimer, and hs-cTnI levels. Tocilizumab has been used with reported success for patients with severe COVID-19 and there are ongoing clinical trials[65-67] and a trial of sarilumab just launched in the United States.[68]

Conclusion

COVID-19, caused by SARS-CoV-2, is a global pandemic evolving in real time. Cardiovascular comorbidities are common in patients with COVID-19 and such patients are at higher risk of morbidity and mortality. However, it is not known if the presence of cardiovascular comorbid conditions pose independent risk or whether this is mediated by other factors (e.g. age). Myocardial injury is present in more than a quarter of critical cases and presents in two patterns: acute myocardial injury and dysfunction on presentation and myocardial injury that develops as illness severity intensifies. The continuation of clinically indicated ACEi and ARB medications

is recommended based on the available evidence at this time. There are a number of promising treatments under investigation, but none with proven clinical efficacy to date.

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Figure Legends

Figure 1. Suspected transmission pathway of SARS-CoV-2 to humans

Figure 2. Symptoms of COVID-19

Figure 3. Myocardial injury during COVID-19 can be explained by two mechanisms.1) From the associated cytokine storm manifested by elevated levels of IL-6, ferritin, LDH, and D-dimer. 2) Myocardial dysfunction from the direct effect of SARS-CoV-2 on the heart.

Figure 4. SARS-CoV-2 binds to the ACE2 receptor following activation of the spike protein by TMPRSS2