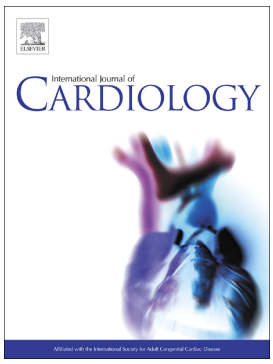

The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease

Weiyi Tan, Jamil Aboulhosn

PII: S0167-5273(20)31593-X

DOI: https://doi.org/10.1016/j.ijcard.2020.03.063

Reference: IJCA 28465

To appear in: *International Journal of Cardiology*

Please cite this article as: W. Tan and J. Aboulhosn, The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease, *International Journal of Cardiology* (2020), https://doi.org/10.1016/j.ijcard.2020.03.063

Title: The Cardiovascular Burden of Coronavirus Disease 2019 (COVID-19) with a Focus on Congenital Heart Disease

Author Names and Affiliations:
Weiyi Tan[a], MD, MPH
Jamil Aboulhosn[a], MD

[a] Ahmanson/UCLA Adult Congenital Heart Center, Los Angeles, California
100 UCLA Medical Plaza, Suite 630 East
Los Angeles, California, USA, 90095

Corresponding Author:
Weiyi Tan, MD, MPH
Ahmanson/UCLA Adult Congenital Heart Center, Los Angeles, California
100 UCLA Medical Plaza, Suite 630 East
Los Angeles, California, USA, 90095
weiyitan@mednet.ucla.edu

Abstract:

Coronavirus disease 2019 (COVID-19), caused by a novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first described in a cluster of patients presenting with pneumonia symptoms in Wuhan, China, in December of 2019. Over the past few months, COVID-19 has developed into a worldwide pandemic, with over 400,000 documented cases globally as of March 24th, 2020. The SARS-CoV-2 virus is most likely of zoonotic origin, but has been shown to have effective human-to-human transmission. COVID-19 results in mild symptoms in the majority of infected patients, but can cause severe lung injury, cardiac injury, and death. Given the novel nature of COVID-19, no established treatment beyond supportive care exists currently, but extensive public-health measures to reduce person-to-person transmission of COVID-19 have been implemented globally to curb the spread of disease, reduce the burden on healthcare systems, and protect vulnerable populations, including the elderly and those with underlying medical comorbidities. Since this is an emerging infectious disease, there is, as of yet, limited data on the effects of this infection on patients with cardiovascular disease, particularly so for those with congenital heart disease. We summarize herewith the early experience with COVID-19 and consider the potential applicability to and implications for patients with cardiovascular disease in general and congenital heart disease in particular.

Introduction:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel betacoronavirus that was first described in a cluster of patients presenting with pneumonia symptoms in Wuhan, China (1) in December of 2019. Two previous epidemics caused by betacoronaviruses, severe acute respiratory syndrome coronavirus (SARS-CoV) (2) and Middle East respiratory syndrome coronavirus (MERS-CoV) (3), presaged the potential that another betacoronavirus was likely to cause a widespread pandemic (4). By the time the first paper documenting this novel coronavirus infection was published on January 24, 2020, the infection had spread to over 800 patients, with evidence of person-to-person transmission (5) as well as international cases. Over the past few months, the disease caused by SARS-CoV-2, coronavirus disease 2019 (COVID-19), has now become a worldwide pandemic, with over 400,000 cases globally. Since this is an emerging infectious disease, there is, as of yet, a paucity of data about the effects of this infection on patients with congenital heart disease. We aim to summarize the initial experience with COVID-19 and consider the potential applicability to and implications for patients with congenital heart disease.

Background:

Viral effects on the heart and on patients with cardiovascular conditions.

Based on data from influenza viral infections and the previous coronavirus epidemics (SARS and MERS), these viral infections mainly cause pulmonary issues like pneumonia and acute respiratory distress syndrome (2,3). That being said, these viruses have been shown to cause direct myocardial injury, as there are known cases of myocarditis caused by both influenza and coronaviruses (6–8). Furthermore, patients with underlying heart disease (both congenital or acquired) seem to have increased morbidity and mortality related to viral infections (9,10), and that is why there is a strong recommendation to vaccinate against influenza to prevent poor outcomes in them(11,12). There is also some data to suggest that patients with underlying heart disease may be more susceptible to contracting coronavirus infection(13).

SARS-CoV-2:

Human Infection

SARS-CoV-2 has a genome identity of 96% to a bat SARS-like coronavirus, and thus most likely a zoonotic origin (14,15). The betacoronaviruses are able to infect human hosts through angiotensin converting enzyme 2 (ACE2) (4,15,16) (Figure 1). ACE2 is a membrane-bound protein that is expressed in many human cells, including vascular endothelia, renal tissue, cardiovascular tissue, and small intestine epithelia (16). Based on studies investigating both SARS and MERS coronaviruses, it was shown back in 2015 that circulating bat coronaviruses have the potential for human emergence using human ACE2 as a receptor into host cells (4). Phylogenetic analysis of SARS-CoV-2 demonstrates that this novel betacoronavirus has a very similar receptor binding domain/motif to the SARS coronavirus (15), suggesting that SARS-CoV-2 uses ACE2 as a receptor to enter human cells. Recent genetic sequence analysis of SARS-CoV-2 shows an 80% similarity to SARS and a 50% similarity to MERS coronavirus,

making SARS-CoV-2 the seventh member of the coronavirus family that infects humans, as well as the third coronavirus with bat origins (17).

Human-to-Human Transmission

SARS-CoV-2 has been shown to be transmitted via human-to-human contact with an estimated R_0 of between 2-3 (18). The betacoronaviruses mainly infect epithelial cells in the lung (19), but SARS-CoV-2 has been detected in respiratory, fecal, and blood specimens of patients infected with the virus (14). SARS-CoV-2 is spread through droplets, contact, and entry through ocular tissue (20). Fecal shedding has been seen in up to 30% of patients for up to 4-5 weeks after onset of symptoms, but it is unclear if this correlates with infectivity. Since ACE2 is also expressed in intestinal epithelia and live virus has been detected in the stool of patients with COVID-19, transmission via the fecal-oral route is theoretically possible, but has not been confirmed in epidemiologic studies as of yet (20). The virus can remain viable as an aerosol for up to 3 hours and on certain surfaces for up to 72 hours (21). The virus can be detected 1-2 days prior to symptom onset in upper respiratory samples (20), and with a median incubation period estimate of 5.1 days (95% CI, 4.5 to 5.8 days) (18,22), SARS-CoV-2 is thought to be mainly spread via asymptomatic carriers (23,24), which makes containment of the disease difficult. Substantial undocumented infections by asymptomatic but infected individuals may explain the rapid geographic spread of COVID-19 (25).

Pathophysiology

One case report highlights a patient who underwent post-mortem autopsy for pathological analysis (26). In that study, SARS-CoV-2 was shown to cause direct damage to pneumocytes via a viral cytopathic effect, but also caused acute respiratory distress syndrome (ARDS) characterized by diffuse alveolar damage (26). No direct damage to heart tissue was noted, but this was only in one patient. Data from multiple studies show that inflammatory markers are increased with SARS-CoV-2 infection, ranging from CRP, IL-6, IFN-γ, to TNF-α (1,27,28), which has been posited to contribute to a sustained inflammatory response and cytokine storm (Figure 1). Lymphopenia is commonly seen in patients who are critically ill (29), suggesting that SARS-CoV-2 viral particles can invade lymphocytes and cause targeted destruction of these cells.

To summarize, SARS-CoV-2 causes direct damage to lung epithelia, which can lead to severe pneumonia and ARDS. The COVID-19 virus also causes an inflammatory response in infected patients, which may lead to multi-organ failure and disseminated intravascular coagulation (DIC) in certain patients (30). Furthermore, the hypoxia seen in patients with severe pneumonia and ARDS may also lead to further end-organ dysfunction/damage and death in critically-ill patients (29).

Signs and Symptoms

There appears to be two clinical stages to the disease. The first stage is the replicative stage, when SARS-CoV-2 is replicating over the course of several days and the patient presents with relatively mild symptoms. Unlike other human coronavirus infections, COVID-19 does not commonly present with upper respiratory symptoms like rhinorrhea (5). One study showed that a sizeable proportion (18%) of patients who are infected with COVID-19 may not exhibit any symptoms at all (24). Most symptomatic patients with COVID-19 will present with fever, dry cough, and shortness of breath. They will have

findings of pneumonia on chest x-ray and computed tomography scans of the chest (31). Most symptomatic patients suffer a mild respiratory infection requiring supportive care like supplemental oxygen. Patients can also develop gastrointestinal symptoms like abdominal pain, nausea, and diarrhea (32). As mentioned earlier, lymphopenia is seen commonly in patients with COVID-19 and may be a poor prognostic factor (31,32).

The second stage is the adaptive immunity stage, when the body develops an antibody response to the virus. This leads to falling titers of the virus and resolution of symptoms in most patients. There is a minority of patients, however, that become critically-ill and have a high risk of mortality. Around 10% of patients will have worsening of disease requiring intensive care (Table 1). They can suffer from ARDS, viremia, acute cardiac injury, multi-organ failure, and secondary bacterial infections (1). The multi-organ dysfunction is believed to be secondary to a marked immune inflammatory response (33).

COVID-19 and Cardiovascular Involvement

COVID-19 and Myocardial Injury

COVID-19 may result in cardiac injury via multiple mechanisms (Figure 1):

1. COVID-19 may cause cardiac injury indirectly due to an overwhelming immune inflammatory response and cytokine storm (33).
2. SARS-CoV-2 viral invasion of cardiomyocytes and direct damage via this process, but this has not been proven in pathology studies (26).
3. Severe hypoxia from acute respiratory damage caused by the virus may result in oxidative stress and myocardial injury from increased myocardial oxygen demand in the presence of severe hypoxia due to acute lung injury (ARDS).

Furthermore, ACE2 is expressed in the heart, and the SARS-CoV-2 virus uses this enzyme as a receptor for entry into the cell (15,16). It is unclear at this time, however, if SARS-CoV-2 binding alters ACE2 expression or causes dysregulation of the RAAS (renin-angiotensin-aldosterone system) pathway.

While the mechanism of cardiac injury is not fully described, there are data documenting COVID-19 and its effects on the cardiovascular system. In two studies, cardiac injury (manifested as an increase in troponin levels) was found in 8% of admitted patients (Table 1). While an uncommon finding overall, cardiac injury was more common in critically-ill patients (32). Two studies of critically-ill patients demonstrated that 23% (n=12) of patients developed cardiac injury (29) and 33% (n=7) of patients developed a cardiomyopathy (34). Another study documented that among a group of patients (n = 120) with COVID-19, elevations in troponin levels (n = 12, 10%) and N-terminal pro B-type natriuretic peptide levels (n = 33, 27.5%) were detected, signaling cardiovascular injury (35).

One analysis of patients who died from COVID-19 demonstrated that patients had two different time points of death. A group of patients died around 14 days after onset of disease and another group died around 22 days after onset (27). The authors hypothesized that the initial group died of respiratory failure, but the second group had myocardial damage and significant cardiovascular collapse concerning for myocarditis (27). There have been a few case reports documenting clinical myocarditis with COVID-19 (36,37). This is consistent with previous reports of myocarditis caused by coronaviruses, including MERS (7,8,27,38). Given the increased elevations of cytokine levels noted in patients with severe COVID-

19 infection, as well as the observation that some patients with COVID-19 deteriorate rapidly with multi-organ failure and cardiogenic shock, more studies should be performed to investigate COVID-19 and its possible role in fulminant myocarditis (35).

COVID-19 and Adult Patients with Cardiovascular Disease

While most patients who contract COVID-19 recover (39), there are those who develop severe or critical illness. Unfortunately, multiple studies have shown that patients with underlying cardiovascular comorbidities, such as hypertension and coronary artery disease, are more likely to suffer from a severe COVID-19 infection that requires ICU care, have complications like ARDS, which in turn may result in death (27–29,32,40). One study showed that patients infected with COVID-19 who had underlying hypertension had increased odds of death (OR 3.05 [95% CI 1.57-5.92, $p < 0.001$]) compared to those without hypertension. Similarly, coronary artery disease was associated with increased odds (OR 21.4 [95% CI 4.64-98.7, $p < 0.0001$]) of death (40). In one meta-analysis, COVID-19 patients with hypertension had a relative risk ratio of 2.03 (95% CI 1.54-2.68, $p < 0.00001$) of having severe disease/requiring ICU care compared to those without hypertension. Patients with coronary artery disease/cerebrovascular disease had a relative risk ratio of 3.3 (95% CI 2.03-5.36, $p < 0.00001$) of having severe disease/requiring ICU care compared to those without cardiovascular disease (41). When analyzing the largest case series to date (44,672 confirmed COVID-19 cases), the Chinese Center for Disease Control and Prevention reported that patients with cardiovascular disease had a case fatality rate of 10.5% and those with hypertension had a case fatality rate of 6%, both of which were higher than the overall case fatality rate of 2.3% (39) (Figure 2). Patients with hypertension accounted for 13% of the COVID-19 cases but they comprised 32% of the COVID-19 deaths. Patients with cardiovascular disease made up 4.2% of the COVID-19 cases, but were responsible for 18.3% of the COVID-19 deaths ((42), Figure 2). This may be due to the fact that patients with history of coronary artery disease or acute coronary syndromes may have reduced or impaired cardiovascular functional reserve, and the COVID-19 infection may either precipitate a myocardial infarction (type 1 myocardial infarction), increase myocardial demand leading to worsening ischemia and necrosis (type 2 myocardial infarction), or increase metabolic demand that leads to heart failure and death (43).

There is a case series of patients with heart transplants and COVID-19 infection (44). It appears that although these patients are immunosuppressed, they seem to have similar outcomes compared to patients without heart transplantation and COVID-19 infection. The number of patients was very small (n=2), and thus results cannot obviously be extrapolated to a larger population. What was remarkable, however, was that of the 200 heart transplant patients in the Hubei province, only three were infected with COVID-19, which speaks to the importance of proper hygiene, social distancing and other public health measures (44) . To date, there are no published reports of patients with congenital heart disease and COVID-19 infection, albeit they are bound to come.

COVID-19 and the Pediatric Patient

There is only limited data detailing the effects of COVID-19 on the pediatric population. A review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that less than 1% of COVID-19 cases were in children younger than 10 years old (39). Based on a single epidemiological study of 2,143 pediatric patients evaluated and treated for COVID-19, there were 731 cases confirmed via RT-

PCR testing (45). Children of all ages were infected, with the median age being 7 years (range 1 day to 18 years). 56% of the infected pediatric patients were male. Compared to adult patients, children diagnosed with COVID-19 seem to have less severe disease. Over 90% of the cases were mild or moderate in nature. Young children, especially infants, however, seemed to be more susceptible to severe disease than older children; 10% of patients under 1 year of age had severe or critical disease. The only death in the series was a 14 year-old male (45).

In another study of 1,391 children under 16 years of age assessed and tested for COVID-19, 171 (12.3%) were positive for SARS-CoV-2 infection. The median age of infected children was 6.7 years. 15.8% of patients had no symptoms or signs of pneumonia. Three (1.8%) children required intensive care and mechanical ventilatory support, but all had pre-existing medical conditions. Lymphopenia was present in only 6 (3.5%) patients. A 10-month-old child with history of intussusception died from multiorgan failure, and this was the only death in the study (46).

A third study examined 366 children under the age of 17 years. In that group, only 6 (1.6%) patients tested positive for COVID-19. The median age of infected patients was 3 years old (range 1-7 years), and none of the infected children had any comorbidities. All six of the pediatric patients had fever and cough at diagnosis, as well as lymphopenia. One of the patients required intensive care unit (ICU) admission, but there were no mortalities.

The mechanism by which children seem less susceptible to severe infection caused by SARS-CoV-2 has yet to be elucidated. It has been theorized that the ACE2 (the binding protein for SARS-CoV-2) in children is not as functional as it is in adults, and thus SARS-CoV-2 is less infectious (45). None of the studies described children with congenital heart disease and COVID-19, and thus the effect of the virus on this specific patient population is not clear. Nevertheless, children seem less vulnerable to COVID-19 than adults overall.

COVID-19 and the Pregnant Patient

A review of pregnant women infected with COVID-19 revealed that pregnant women are not at increased risk of poor outcomes when compared to the general adult population (47), and there seems to be no evidence of vertical transmission of the SARS-CoV-2 virus from mother to baby during birth or during breastfeeding at present (20,47). All the women who gave birth with COVID-19 had cesarean sections, so there is no data about vertical transmission for women who are infected earlier in the pregnancy or who deliver vaginally. More studies are clearly warranted to examine the potential impact of COVID-19 on pregnancy.

COVID-19 and the Adult with Congenital Heart Disease

To date, there are no published studies on COVID-19 in adult patients with congenital heart disease. Thus, all of the current management strategies are extrapolated from what is known about the effect of COVID-19 on adult patients and adult patients with cardiovascular disease. That being said, efforts are under way through the Adult Congenital Heart Association and the International Society of Adult Congenital Heart Disease to gather data on the number of suspected and confirmed cases both in the United States and globally and to better understand outcomes in this population. In the absence of data to help guide care it is difficult to make any definitive recommendations, however, there are some sensible steps that can be taken while we await the building of an evidence base.

Diagnosis

When a patient with congenital heart disease is suspected of having COVID-19, the first step is confirmation of the disease. Nasopharyngeal swab and RT-PCR is the recommended initial test, but it is only about 75% sensitive (48). If the clinical suspicion is high enough, a CT chest may be warranted (49). Proper isolation measures should be taken and providers should wear appropriate personal protective equipment, regardless of the diagnostic test. It should be noted that there are cases of negative initial testing that later repeated as positive, as this may be due to low viral titers early in the infection. One shocking reality is that in many countries, including Western nations like the United States, lack widespread testing capability. At the time of the writing of this manuscript in the third week of March 2020, testing in Los Angeles is woefully unavailable for the vast majority of potentially infected patients. Drive-through testing is not available for days and in-hospital testing is limited to the highest risk subsets. This situation must be remedied and quickly for us to have a realistic chance of accounting for and tracking the degree of spread of this virus.

Risk Stratification

Patients with underlying cardiovascular comorbidities are at increased risk of morbidity and mortality from SARS-CoV-2 infection (39). Studies so far have not detailed in a granular fashion the risk of individual cardiovascular complications in patients with underlying cardiovascular disease who are infected with SARS-CoV-2. While no studies on COVID-19 have included patients with congenital heart disease, it stands to reason that patients with congenital heart disease could be considered at higher risk for complications from COVID-19. Certain adult patients with congenital heart disease (ACHD) are likely at higher risk than others. Based on the ACHD Anatomy and Physiological Stage Classification, any patient with complex congenital heart disease (Anatomy Stage III) or Physiological Stage B, C, or D symptoms could be considered high risk for complications related to COVID-19 infection on the basis of decreased functional reserve (50) (Table 2). Those with reduced immunity, including Down syndrome, DiGeorge syndrome and asplenia may be at even higher risk for poor outcomes with COVID-19 infection. Studies have tried to risk-stratify patients suffering from a viral pneumonia (51), and the MuLBSTA score may be a tool providers can use to see which patients are at high risk of decompensation and death (31).

Prevention

Since patients with underlying cardiovascular disease are at higher risk of morbidity and mortality, patients with ACHD should take great care in preventing infection. This includes frequent handwashing, social distancing measures, proper and appropriate use of masks and other personal protective equipment, and cleaning and disinfecting commonly touched surfaces (52). Patients with congenital heart disease should be vaccinated against influenza and pneumococcal pneumonia (11,12). If possible, regularly scheduled clinic visits should be converted to telehealth visits to minimize risk of acquiring an infection in the nosocomial setting (53). This desire to minimize risk of infection must obviously be weighed against the necessity of in-person visits for some patients, e.g. those with decompensated congestive heart failure or arrhythmias. The advent of wearable technology and wide availability of blood pressure, heart rate, and oximetry equipment for home use can be a reasonable substitute for in-clinic vital sign measurements. Additionally, the video function can allow a clinician to inspect the

patient visually, albeit in a far less comprehensive manner when compared to the traditional physical examination. Hand-held and easily sterilized echocardiographic equipment can also be a 'handy' substitute for traditional comprehensive echocardiography, and the inevitably higher rate of exposure in a frequently visited echo lab. At least in the short term, these social distancing approaches to the practice of clinical medicine will have to suffice for the majority of our patients. Our early experience with telehealth at the UCLA ACHD clinic has been positive and we have been able to safely diminish our physical clinic walkthrough volume.

Management

Once a patient with ACHD is diagnosed with COVID-19, the management of the infection is similar to the general population. Most COVID-19 patients (close to 80% in the Chinese experience) can be managed expectantly at home with self-care measures (39). The initial data from the United States are similar, and estimates are that 20-30% of patients are being hospitalized (54). For those that need to be admitted, the treatment is mainly supportive and should follow the World Health Organization (WHO) guidelines on management of COVID-19 (55). Symptomatic relief with antipyretics, use of supplemental oxygen and management of comorbid conditions are the cornerstones of therapy. The use of antiviral, immune modulating, or antibiotic therapies is at this point not considered standard of care. Controlled trials are ongoing, and we are all anxiously awaiting results and recommendations for treatment of COVID-19.

Some patients with COVID-19 may experience cardiac injury and arrhythmias (32), and employment of echocardiography and cardiac enzymes would seem paramount in this setting (53). Myocardial injury may occur due to a variety of mechanisms, from direct viral invasion of cardiomyocytes, hypoxia due to severe pneumonia leading to ischemic cardiac tissue, or an overwhelming inflammatory response leading to cytokine storm and myocardial dysfunction (Figure 1) (41). This leads to troponin leak and elevations in brain natriuretic peptide (BNP). While laboratory assessment for cardiac injury is not recommended on a routine basis, patients who show signs and symptoms of myocardial injury (ST-segment changes on an electrocardiogram for example), acute coronary syndrome (chest pain), unstable arrhythmias, or heart failure should be evaluated thoroughly. Differentiation between normal cardiac function with increased metabolic demand, acute coronary syndrome, and fulminant myocarditis will be important as each of these clinical scenarios will require a different treatment algorithm. For patients who are deteriorating, judicious use of fluid resuscitation, vasopressors, mechanical ventilation and extracorporeal membrane oxygenation (ECMO) have been successful at supporting patients through critical illness (29,55). While the use of steroids has not been recommended in the general treatment of COVID-19 (55), there have been reports of patients recovering from fulminant myocarditis with intravenous immunoglobulin and steroids (36). More studies will be needed to help parse out which patients will benefit from such therapies.

In terms of medical treatment options, there are currently over 50 studies in various stages of development related to treatment of COVID-19 (clinicaltrials.gov, accessed March 20, 2020). Given the novel nature of the SARS-CoV-2 virus, there are no known effective therapies at this time, but the therapies being studied include antiviral (remdesivir, lopinavir/ritonavir, chloroquine, hydroxychloroquine) and anti-inflammatory (tocilizumab, steroids) agents. The only trial published so far assesses the use of lopinavir-ritonavir in adults hospitalized with COVID-19, and this therapy showed no

benefit beyond standard of care (56). Many of these therapies have cardiovascular side effects, however, and caution must be used when applying them to patients with congenital heart disease. Vaccine development is also underway and is one of the priorities for the WHO moving forward (14).

If patients suffer cardiovascular complications from COVID-19 requiring either percutaneous or surgical intervention, each case must be assessed on an individual basis. Each institution should develop protocols for appropriate triage, isolation, and treatment of COVID-19 patients who may need such interventions. In China, the preference has been to use thrombolytic therapy for patients with acute coronary syndromes (i.e. ST-elevation myocardial infarction) (57), but this has not been the standard of care in the United States. As the pandemic progresses and resources start to become strained, we may be asked to ration certain measures such as intensive care unit beds, mechanical ventilation and extra-corporeal support. It is our sincere hope that it will not come to this in the majority of countries. This concern further underscores the dire importance of slowing the spread of SARS-CoV-2 to allow health care systems to appropriately prepare and manage this crisis without having to resort to rationing of the highest levels of care. Importantly, the clinical need for imaging, invasive and surgical interventions must be weighed against the risk of infecting healthcare workers who may lack the appropriate personal protective equipment at this point in time. Standard operating procedures for use of personal protective equipment and sterilization of catheterization labs and operating rooms should also be developed (53,58).

Use of RAAS inhibitors and COVID-19

The SARS-CoV-2 virus uses ACE2 as a receptor to enter and infect cells (15), and since ACE2 is expressed in many tissues including vascular endothelium and cardiac tissue (16), there has been some hypotheses that the use of ACE-inhibitors and angiotensin receptor 1 blockers (ARBs) may have an effect on the course of COVID-19. ACE2 inactivates angiotensin II, and generates angiotensin 1-7, which is a potent vasodilator (59). In animal models, the ARBs have been shown to increase cardiac ACE2 expression after chronic (> 28 days) treatment (59). Based on studies of the original SARS coronavirus, viral binding to ACE2 leads to ACE2 downregulation, which results in excessive production of angiotensin II by angiotensin converting enzyme (ACE) and decreased quantities of the vasodilator heptapeptide angiotensin 1-7, which can contribute to lung injury and stimulation of the RAAS pathway. Counterintuitively, while ARBs increase the number of ACE2 receptors available for SARS-CoV-2 binding, the overall effect of ARBs may protect against lung injury by reducing angiotensin II production by ACE and by increasing the production of vasodilator angiotensin 1-7 (59). The effect of ACE-inhibitors and ARBs in patients with COVID-19 are not yet known and remain unproven. More studies are required before any recommendations are made about starting or withdrawing ACE-inhibitor and ARB medications. As such, the Heart Failure Society of America, American College of Cardiology, and American Heart Association released a statement recommending continuation of RAAS inhibitors for patients currently taking them for “indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease (60).” This position has also been echoed by the European Society of Cardiology (61).

Future Directions/Next Steps

The global pandemic caused by COVID-19 is just beginning and the number of people infected by the virus is increasing at an exponential rate. While there are no studies currently documenting COVID-19 infections in patients with congenital heart disease, it is highly likely that with over 300,000 cases diagnosed world-wide (as of 3/22/2020) there have already been a number of congenital heart disease patients infected by SARS-CoV-2. It is imperative that individual programs, in concert with regional, national, and global organizations, work together to ensure data are gathered on the number of patients tested, those diagnosed with the infection, and their outcomes. Congenital cardiology programs need to be ready to enroll these patients in study registries and trials. In the words of Winston Churchill, "never 'worry' about action, but only about inaction." We need to be meticulous in our study of this disease, voracious in our appetite to learn its secrets, and tireless in our efforts to combat its spread.

Tables and Figures:

Table 1: Summary of Initial Cohort Studies of COVID-19 in China.

Author	Journal	Date published	Number of Patients in Study	Age, years (range)	Male, n (%)	Hypertension, n (%)	Cardiovascular Disease, n (%)	Lymphopenia, n (%)	ICU admission, n (%)	Death, n (%)	ARDS, n (%)	Shock, n (%)	Cardiac Injury, n (%)	Arrhythmia, n (%)
Huang, et al	Lancet	1/24/2020	41	49 (41-58)	30 (73%)	6 (15%)	6 (15%)	26 (63%)	13 (32%)	6 (15%)	12 (29%)	3 (7%)	5 (12%)	n/a
Chen, et al.	Lancet	1/29/2020	99	55 (21-82)	67 (68%)	n/a	40 (40%)	35 (35%)	23 (23%)	11 (11%)	17 (17%)	4 (4%)	n/a	n/a
Wang, et al.	JAMA	2/7/2020	138	56 (42-68)	75 (54%)	43 (31%)	20 (15%)	97 (70%)	36 (26%)	6 (4%)	27 (20%)	12 (9%)	10 (7%)	23 (17%)
Xu, et al.	BMJ	2/13/2020	62	41 (32-52)	35 (56%)	5 (8%)	0 (0%)	26 (42%)	1 (2%)	0 (0%)	1 (2%)	n/a	n/a	n/a
Guan, et	NEJM	2/28/2	1099	47 (35-	637 (58	165 (15%	27 (2.5%	731 (83%	55 (5%	15 (1.	37 (3.4	12 (1.	n/a	n/a

al.		020		58)	%)	)	)	)	)	4%)	%)	1%)		
Young, et al.	JAMA	3/3/2020	18	47 (31-73)	9 (50%)	4 (22%)	0 (0%)	7 (39%)	2 (11%)	0 (0%)	1 (5%)	n/a	n/a	n/a
Wu, et al.	JAMA IM	3/13/2020	201	51 (43-60)	128 (64%)	39 (19%)	8 (4%)	126 (64%)	53 (26%)	44 (22%)	84 (42%)	n/a	n/a	n/a
Totals, n (%)			1658	49.4	981 (59%)	262 (17%)	101 (6%)	1048 (63%)	183 (11%)	82 (5%)	179 (11%)	31 (2%)	15 (8%)	23 (17%)

Table 2: Adult Congenital Patients that are likely at higher risk of poor outcomes with COVID-19 due to impaired functional reserve (adapted from 2018 ACC/AHA Guidelines on ACHD patients).

Complex Congenital Anatomy	Any patient with congenital heart disease, regardless of the complexity of the anatomy.		
All Physiological Stages (A through D)	Physiological Stage B	Physiological Stage C	Physiological Stage D
• Cyanotic Heart Defects (Unrepaired or palliated) • Double-outlet ventricle • Fontan Procedure • Interrupted aortic arch • Mitral atresia • Single Ventricle (including double inlet left ventricle, tricuspid atresia, hypoplastic left heart, any other abnormality with a functionally single ventricle) • Pulmonary atresia • Transposition of the Great Arteries (both d-TGA and l-TGA) • Truncus arteriosus • Other abnormalities of atrioventricular and ventriculoarterial connection (i.e. crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)	• NYHA FC II symptoms • Mild hemodynamic sequelae • Mild valvular disease • Trivial or small shunt • Arrhythmia not requiring treatment • Abnormal objective cardiac limitation to exercise	• NYHA FC III symptoms • Significant valvular disease; moderate or greater ventricular dysfunction • Moderate aortic enlargement • Venous or arterial stenosis. • Mild-moderate hypoxemia/cyanosis • Hemodynamically significant shunt • Arrhythmias controlled with treatment • Mild-Moderate Pulmonary hypertension • End-organ dysfunction that is responsive to therapy.	• NYHA FC IV symptoms • Severe aortic enlargement • Arrhythmias refractory to treatment • Severe hypoxemia (associated with cyanosis) • Severe pulmonary hypertension • Eisenmenger syndrome • Refractory end-organ dysfunction

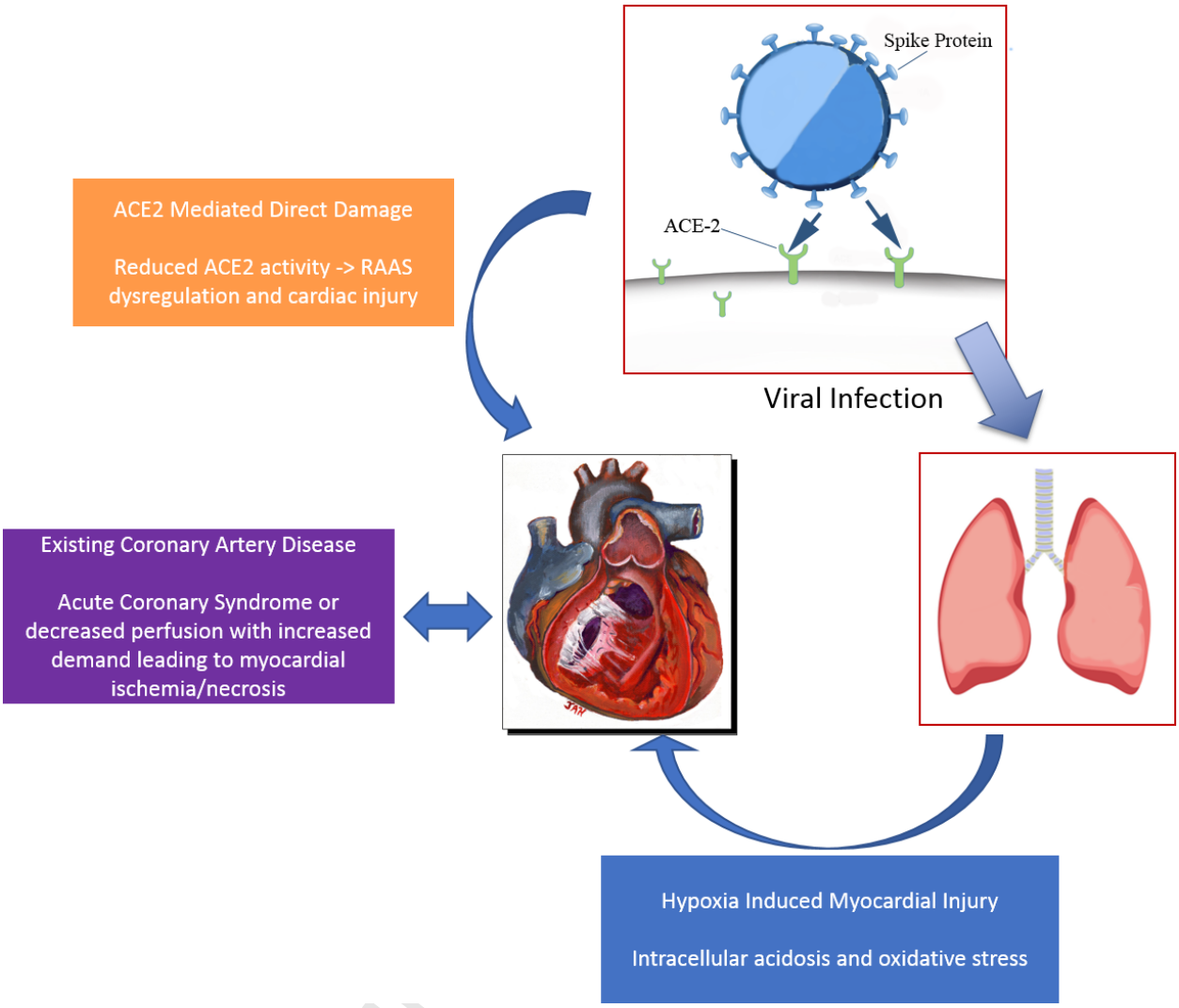

Figure 1. Possible mechanisms of cardiac injury with COVID-19.

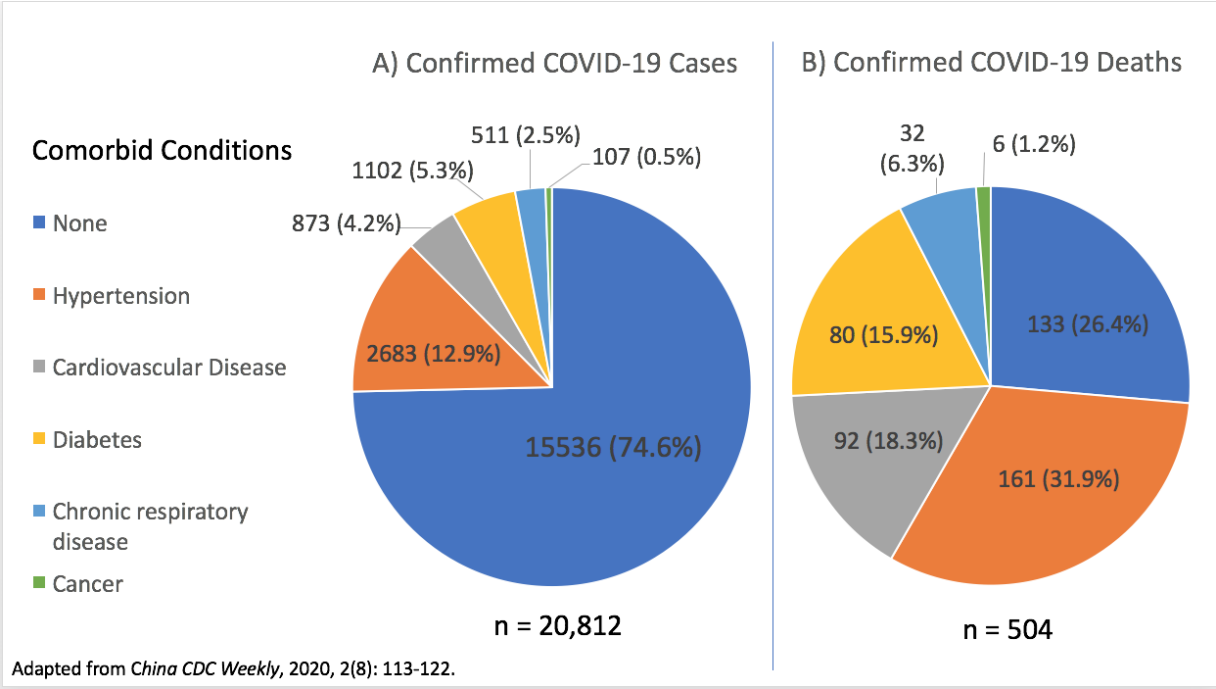

Figure 2. A) Proportion of patients and their comorbid conditions that were diagnosed with COVID-19. B) Proportion of patients and their comorbid conditions that died from COVID-19. This figure was adapted from data from the weekly report from the Chinese Center of Disease Control and Prevention.

References:

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506.
2. Ksiazek TG, Erdman D, Goldsmith CS, et al. A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome. N Engl J Med [Internet]. 2003 May 15;348(20):1953–66. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa030781
3. Zaki AM, Van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814–20.
4. Menachery VD, Yount BL, Debbink K, et al. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. Nat Med. 2015;21(12):1508–13.
5. Wang C, Horby PW, Hayden FG, et al. A novel coronavirus outbreak of global health concern. Lancet. 2020;395(10223):470–3.
6. Ukimura A, Satomi H, Ooi Y, et al. Myocarditis Associated with Influenza A H1N1pdm2009. Influenza Res Treat. 2012;2012:1–8.
7. Rao S, Sasser W, Diaz F, et al. Coronavirus Associated Fulminant Myocarditis Successfully Treated With Intravenous Immunoglobulin and Extracorporeal Membrane Oxygenation. Chest [Internet]. 2014;146(4):336A. Available from: http://dx.doi.org/10.1378/chest.1992018
8. Alhogbani T. Acute myocarditis associated with novel Middle East respiratory syndrome coronavirus. Ann Saudi Med. 2016;36(1):78–80.
9. Gilca R, de Serres G, Boulianne N, et al. Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. Influenza Other Respi Viruses. 2011;5(4):247–55.
10. Yu CM, Wong RSM, Wu EB, et al. Cardiovascular complications of severe acute respiratory syndrome. Postgrad Med J. 2006;82(964):140–4.
11. Bare I, Crawford J, Pon K, et al. Frequency and Consequences of Influenza Vaccination in Adults With Congenital Heart Disease. Am J Cardiol [Internet]. 2018;121(4):491–4. Available from: https://doi.org/10.1016/j.amjcard.2017.11.008
12. Lui GK, Saidi A, Bhatt AB, et al. Diagnosis and management of noncardiac complications in adults with congenital heart disease: A scientific statement from the American Heart Association. Vol. 136, Circulation. 2017.
13. Bastien N, Robinson JL, Tse A, et al. Human coronavirus NL-63 infections in children: A 1-year study. J Clin Microbiol. 2005;43(9):4567–73.
14. Aylward, Bruce (WHO); Liang W (PRC). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). 2020;2019(February):16–24. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
15. Wan Y, Shang J, Graham R, et al. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. J Virol. 2020;(March):1–9.
16. Jia HP, Look DC, Shi L, et al. ACE2 Receptor Expression and Severe Acute Respiratory Syndrome Coronavirus Infection Depend on Differentiation of Human Airway Epithelia. J Virol. 2005;79(23):14614–21.
17. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19)

outbreak. J Autoimmun [Internet]. 2020;(February):102433. Available from: https://doi.org/10.1016/j.jaut.2020.102433

18. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N Engl J Med. 2020;1–9.
19. Fehr AR, Perlman S. Coronaviruses: An Overview of Their Replication and Pathogenesis. In 2015. p. 1–23. Available from: http://link.springer.com/10.1007/978-1-4939-2438-7_1
20. Yang H. The transmission and diagnosis of 2019 novel coronavirus infection disease (COVID-19): A Chinese perspective. J Med Virol [Internet]. 2019;(1):0–2. Available from: http://dx.doi.org/10.1002/jmv.25749
21. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med [Internet]. 2020 Mar 17;NEJMc2004973. Available from: http://www.nejm.org/doi/10.1056/NEJMc2004973
22. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med [Internet]. 2020;2019. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32150748
23. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA [Internet]. 2020 Feb 21;19–20. Available from: https://jamanetwork.com/journals/jama/fullarticle/2762028
24. Mizumoto K, Kagaya K, Zarebski A, et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance [Internet]. 2020;25(10):2000180. Available from: https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.10.2000180
25. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (COVID-19). medRxiv. 2020;3221(March):2020.02.14.20023127.
26. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med [Internet]. 2020;2600(20):19–21. Available from: http://dx.doi.org/10.1016/S2213-2600(20)30076-X
27. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32125452
28. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med [Internet]. 2020;1–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32167524
29. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;2600(20):1–7.
30. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med [Internet]. 2020;1–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32109013
31. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet [Internet]. 2020;395(10223):507–13. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30211-7
32. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel

Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc. 2020;323(11):1061–9.
33. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. Jama [Internet]. 2020;1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32125362
34. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients With COVID-19 in Washington State. JAMA [Internet]. 2020 Mar 19;4720:2019–21. Available from: https://jamanetwork.com/journals/jama/fullarticle/2763485
35. Chen C, Zhou Y, Wang DW. SARS-CoV-2: a potential novel etiology of fulminant myocarditis. Herz [Internet]. 2020 Mar 5;10–2. Available from: http://link.springer.com/10.1007/s00059-020-04909-z
36. Hu H, Ma F, Wei X, et al. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J [Internet]. 2020 Mar 16;1307800. Available from: https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehaa190/5807656
37. Zeng J, Liu Y, Yuan J, et al. First case of COVID-19 infection with fulminant myocarditis complication : case report and insights. 2020;(March).
38. Alexander LK, David Small J, Edwards S, et al. An experimental model for dilated cardiomyopathy after rabbit coronavirus infection. J Infect Dis. 1992;166(5):978–85.
39. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Jama [Internet]. 2020;2019:3–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32091533
40. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet [Internet]. 2020 Mar;6736(20):1–9. Available from: http://dx.doi.org/10.1016/S0140-6736(20)30566-3
41. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol [Internet]. 2020;(0123456789):10.1007/s00392-020-01626–9. Available from: https://pubmed.ncbi.nlm.nih.gov/32161990
42. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi [Internet]. 2020;41(2):145–51. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32064853
43. Zheng Y-Y, Ma Y-T, Zhang J-Y, et al. COVID-19 and the cardiovascular system. Nat Rev Cardiol [Internet]. 2020; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32139904
44. Li F, Cai J, Dong N. First Cases of COVID-19 in Heart Transplantation From China. J Hear Lung Transplant [Internet]. 2020; Available from: https://doi.org/10.1016/j.healun.2020.03.006
45. Dong Y, Mo X, Hu Y, et al. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. Pediatrics [Internet]. 2020 Mar 16;e20200702. Available from: http://pediatrics.aappublications.org/lookup/doi/10.1542/peds.2020-0702
46. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. N Engl J Med [Internet]. 2020 Mar 18;NEJMc2005073. Available from: http://www.nejm.org/doi/10.1056/NEJMc2005073
47. Yang H, Wang C, Poon LC. Novel coronavirus infection and pregnancy. 2020;10–2.

48. Fang Y, Zhang H, Xie J, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology [Internet]. 2020 Feb 19;2013(1976):200432. Available from: http://pubs.rsna.org/doi/10.1148/radiol.2020200432
49. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology [Internet]. 2020;2019:200642. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32101510
50. Stout KK, Daniels CJ, Aboulhosn JA, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol [Internet]. 2019;73(12):e81–192. Available from: https://doi.org/10.1016/j.jacc.2018.08.1029
51. Guo L, Wei D, Zhang X, et al. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. Front Microbiol. 2019;10(December):1–10.
52. National Center for Immunization and Respiratory Diseases (NCIRD) D of VD. Coronavirus Disease 2019 (COVID-19). "How to Protect Yourself" [Internet]. 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prepare/prevention.html
53. Bulletin ACCC. COVID-19 Clinical Guidance For the Cardiovascular Care Team. :1–4.
54. Bialek S, Boundy E, Bowen V, et al. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep [Internet]. 2020 Mar 18;69(12):16–9. Available from: http://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm?s_cid=mm6912e2_w
55. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Who [Internet]. 2020;(January):12. Available from: https://www.who.int/internal-publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected%0Ahttp://apps.who.int/iris/bitstream/10665/178529/1/WHO_MERS_Clinical_15.1_eng.pdf
56. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;1–13.
57. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) [Internet]. Available from: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html
58. Wong J, Goh QY, Tan Z, et al. Preparing for a COVID-19 pandemic: a review of operating room outbreak response measures in a large tertiary hospital in Singapore. Can J Anesth Can d'anesthésie [Internet]. 2020;1–14. Available from: http://link.springer.com/10.1007/s12630-020-01620-9
59. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020;(February):2–5.
60. Society HF, Kovacs RJ. HFSA / ACC / AHA Statement Addresses Concerns Re : Using RAAS Antagonists in. 2020;17–20.
61. Simone G de. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers [Internet]. 2020 [cited 2020 Mar 20]. Available from: https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang

The Cardiovascular Burden of Coronavirus Disease 2019 (COVID-19) with a Focus on Congenital Heart Disease Highlights

- The global COVID-19 pandemic is caused by a novel coronavirus, SARS-CoV-2.
- COVID-19 results in respiratory illness, but some patients can have cardiac injury.
- Patients with underlying cardiac disease have worse outcomes with COVID-19
- ACHD patients may be at increased risk of worse outcomes with COVID-19
- No treatment exists currently, the focus is on supportive care and prevention.