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Myocardial injury and COVID-19: Possible mechanisms

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) has quickly progressed to a global health emergency. Respiratory illness is the major cause of morbidity and mortality in these patients with the disease spectrum ranging from asymptomatic subclinical infection, to severe pneumonia progressing to acute respiratory distress syndrome. There is growing evidence describing pathophysiological resemblance of SARS-CoV-2 infection with other coronavirus infections such as Severe Acute Respiratory Syndrome coronavirus and Middle East Respiratory Syndrome coronavirus (MERS-CoV). Angiotensin Converting Enzyme-2 receptors play a pivotal role in the pathogenesis of the virus. Disruption of this receptor leads to cardiomyopathy, cardiac dysfunction, and heart failure. Patients with cardiovascular disease are more likely to be infected with SARS-CoV-2 and they are more likely to develop severe symptoms. Hypertension, arrhythmia, cardiomyopathy and coronary heart disease are amongst major cardiovascular disease comorbidities seen in severe cases of COVID-19. There is growing literature exploring cardiac involvement in SARS-CoV-2. Myocardial injury is one of the important pathogenic features of COVID-19. As a surrogate for myocardial injury, multiple studies have shown increased cardiac biomarkers mainly cardiac troponins I and T in the infected patients especially those with severe disease. Myocarditis is depicted as another cause of morbidity amongst COVID-19 patients. The exact mechanisms of how SARS-CoV-2 can cause myocardial injury are not clearly understood. The proposed mechanisms of myocardial injury are direct damage to the cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, interferon mediated immune response, exaggerated cytokine response by Type 1 and 2 helper T cells, in addition to coronary plaque destabilization, and hypoxia.

1. Introduction

The current outbreak of the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the cause of Coronavirus Disease 2019 (COVID-19) has quickly progressed to a global health emergency. As of April 2020, very few countries remain unfamiliar with the devastation of the virion's consequences. According to the Johns Hopkins COVID-19 Resource Center, 2 million people worldwide have been infected with the virus as of 16 April 2020 since its origin in December 2019 [1,2]. At this point, the organ involvement of COVID-19 appears to be primarily respiratory with a range of disease severity. The range includes asymptomatic subclinical infection, or mild upper respiratory tract illness to nonlife-threatening pneumonia to severe pneumonia progressing to acute respiratory distress syndrome (ARDS) requiring intensive care, mechanical ventilation, and extracorporeal membrane oxygenation [3]. However, much is unknown

about the extrapulmonary manifestations of the disease. Currently, evidence has suggested gastrointestinal and hepatic involvement as well as cardiac complications such as myocarditis from SARS-CoV-2 [4–7].

Since the 1960s, multiple human coronaviruses have been identified, which usually cause mild, self-limiting disease. However, there are also more lethal forms including Severe Acute Respiratory Syndrome coronavirus, Middle East Respiratory Syndrome coronavirus (MERS-CoV), and of course the current SARS-CoV-2 [8]. Corona, meaning “crown” or “garland” in Latin was used to describe this virus when it was first seen due to its spike-like capsid [9]. Importantly, these spikes have demonstrated binding capability to the metallo-peptidase, Angiotensin Converting Enzyme-2 (ACE-2) in a study by Li et al. done over a decade ago in an attempt to better understand the behavior of the SARS-CoV subfamily [10]. Inspired by this finding, other groups such as Hamming et al. explored the expression pattern of ACE-2 and noted that

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its presence in lung alveolar epithelial cells, small intestine epithelial cells, arterial and venous endothelial cells, and smooth muscle cells [11]. The variety of ACE-2 tissue expression further suggests the correlation between SARS-CoV-2 and extrapulmonary manifestations.

Cardiovascular manifestations are not unique to this coronavirus pandemic. In 2016 a case report documented a patient infected with MERS-CoV who was found to have acute heart failure secondary to myocarditis confirmed by cardiac MRI [12]. Before then, in 2009, Oudit et al. suggested that the interaction between the SARS-CoV subfamily and ACE-2 mediated myocardial damage leading to systolic dysfunction and arrhythmias [13–16]. While much remains unclear about this new coronavirus strain, SARS-CoV-2, case reports similar to those of past outbreaks suggesting cardiac involvement have begun to emerge [12,39,40]. In addition, these more recent reports have suggested that patients experiencing myocardial injury from SARS-CoV-2 have a significantly higher risk of in-hospital mortality [17]. Given the prevalence and apparent impact on patient outcomes with COVID-19, this paper aims to review the effects of the novel virus on the cardiovascular system, including its relationship with myocardial damage.

2. Comorbid cardiovascular disease and illness course

It is not known how underlying cardiovascular disease (CVD) contributes to the severity of COVID-19 disease. Does comorbid CVD increase the likelihood of developing severe disease and/or increase the risk of myocardial injury? Lessons from SARS and MERS are unclear with regard to the impact of CVD on disease severity. A meta-analysis of 637 cases of MERS identified the prevalence of CVD, hypertension, and diabetes to be 30%, 50%, and 50% respectively [18]. Authors suggest that metabolic syndrome-related conditions, such as CVD, may predispose patients to increased risk for MERS infection through increased systemic inflammation and dysregulation of the immune system. While it is intuitive that the underlying cardiovascular disease burden may decrease the body's reserve to fight a severe infection, the data is far from definitive.

Many recent studies have indicated CVD as a risk factor for severe COVID-19 disease [19–21]. A summary of 44,672 COVID-19 cases documented by the Chinese Center for Disease Control and Prevention demonstrated a case fatality rate of 10.5% with comorbid CVD compared to a 2.4% overall case fatality rate [2]. A meta-analysis by Bo Li et al. of 1527 patients mostly in Wuhan, China indicated the prevalence of hypertension, cardiac and cerebrovascular disease, and diabetes to be 17.1%, 16.4%, and 9.7% respectively amongst patients with COVID-19. A sub-group analysis showed that cardiac and cerebrovascular disease was present in 16.7% of cases requiring ICU admission, while only 6.2% of non-ICU cases [20]. A recent retrospective study by Guo et al. in a single center in Wuhan, China examined mortality associated with CVD comorbidity and troponin T (TnT) elevation on admission [22]. In this study, CVD was defined as patients with hypertension, coronary artery disease, or cardiomyopathy. Comorbid CVD and elevated (TnT) was associated with the highest mortality of 69.4%, elevated TnT without underlying CVD was 37.5%, comorbid CVD without TnT elevation was 13.3%, compared to 7.6% for individuals without CVD or TnT elevations on admission. Importantly, individuals with CVD were significantly more likely to experience elevated TnT on admission compared to patients without underlying disease, indicating an increased susceptibility to cardiac tissue insult due to underlying chronic disease.

Various mechanisms have been suggested to explain the increased vulnerability of patients with underlying CVD for severe COVID-19 disease. One mechanism, direct myocardial injury, will be addressed subsequently in this review. Other proposed mechanisms include: 1) Ineffective adaptation of the cardiovascular system to the increased demand of severe viral illness, coupled with decreased systemic oxygenation during pneumonia [23–25]. 2) Immune dysregulation, including T cell and immune signaling dysfunction, recognized as an important factor in the pathogenesis of vascular disease, may also

adversely affect the body's response to SARS-CoV-2 infection [26–29]. 3) Electrolyte imbalances and adverse medication effects may disproportionately challenge a diseased heart, with special consideration for the regimen of hydroxychloroquine and azithromycin treatment due to the potential for QTc prolongation [5,30]. Future studies are needed to elucidate these mechanisms and continue to identify targeted interventions for patients with underlying CVD.

3. Myocardial injury

Cardiac dysfunction is not a common sequela of COVID-19 disease. However, myocardial injury has been noted in a significant number of infected patients, and it would not be the first time a coronavirus was associated with cardiac complications. With previous SARS infections, patients have developed systolic and diastolic dysfunction with subsequent heart failure, arrhythmias, and sudden death due to myocardial injury [14,15]. In a study by Li et al. patients experiencing acute phase infection of SARS demonstrated impaired left ventricular performance observed via echocardiography [14]. A study by Yu et al. showed that in a cohort of 121 SARS infected patients there was documented tachycardia despite being afebrile and disease resolution, hypotension, bradycardia, and cardiomegaly during their disease courses [15]. While many of these complications were self-limiting, it demonstrates the propensity for the SARS coronavirus subfamily to infect and modulate cardiac tissue potentiating myocardial damage.

The evidence implicating the SARS-CoV-2 as a cause of myocardial damage appears to be more concrete when compared to its SARS ancestors. In a cross-sectional study by Chen et al., factors including elevated NT-proBNP, elevated cTnI, elevated hs-CRP, which are markers of myocardial injury and inflammation respectively, were significantly correlated with severe disease and critical illness. They further noted that age, male sex, elevated serum creatinine, hypertension, and coronary heart disease are additional factors contributing to severity of disease [31]. In one of the initial studies in Wuhan, Huang et al., reported increased high sensitive troponin I (hs-cTnI) levels (> 28 pg/ml) in 5 of 41 COVID-19 patients. In their study 4 out of 5 patients with elevated hs-cTnI required ICU admission [32]. In a similar single-center case series of 138 patients, 36 patients required ICU admission and their levels of creatine kinase (CK)-MB and hs-cTnI were significantly higher [33]. Similarly, in a retrospective Chinese case series study on 187 patients with confirmed cases of COVID-19, nearly 27% demonstrated increased TnT levels consistent with myocardial injury. As mentioned previously in *Comorbid Cardiovascular Disease and Illness Course*, this study demonstrated that in patients with underlying CVD increased TnT levels were associated with higher mortality compared with no CVD. However, even in patients without underlying CVD, elevated troponin was associated with higher mortality. Furthermore, they noted that frequency of arrhythmias was higher in patients with elevated TnT. Finally they reported that in patients who died from the virus, levels of TnT and NT-proBNP increased during the course of hospitalization [22]. In a similar study in Wuhan a total of 82 out of 416 hospitalized patients showed myocardial injury via the same surrogate markers and the mortality rate was higher in this group of patients even after adjustment for age and other comorbidities [34]. In another case-series of 419 cases with COVID-19 in Shenzhen, China, patients were divided into 36 ICU patients and 383 non-ICU patients. They reported that hs-cTnI level was significantly higher in the ICU group. Patients with elevated enzymes or cardiac symptoms underwent echocardiography demonstrating thickened interventricular septum in 11 (31%) patients with associated enlarged left ventricular diastolic diameter, decreased left ventricular ejection fraction, and increased pulmonary arterial pressure in 4 (11%) patients [35]. Additionally, a Chinese case series by Ruan et al. on the current SARS-CoV-2, analyzed mortality data of 150 patients. 5 out of 68 patients that succumbed to the virus had myocardial damage leading to circulatory failure reported as the cause of death. Further, 22 out of the 68 deceased patients showed respiratory

failure accompanied by myocardial damage. In accordance with the previously mentioned studies, cardiac troponin and myoglobin levels in the death group were significantly higher than the discharge group [36]. Given the clinical data, the group suspected that the course of death in some of these patients was due to fulminant myocarditis.

Myocarditis is a specific clinical sequela of myocardial damage, and it can be diagnosed histologically or clinically. Clinical diagnosis can be made, for instance, via the 2013 European Society of Cardiology's position statement which requires a clinical presentation such as chest pain, for example, as well as a diagnostic criterion like elevated TnT or TnI [37]. It should be noted, though, that some clinicians may use different criteria for diagnosis, and this may affect incidence between studies. Regardless, viral infection has been noted to be one of the most common causes of myocarditis [38]. Further, fulminant myocarditis defines an acute myocarditis episode, as opposed to chronic myocarditis, where the patient experiences life threatening cardiogenic shock. Since the Ruan et al. study, multiple clinicians have published case reports on patients diagnosed with myocarditis who are COVID-19 positive. In two cases, the patients presented with only cardiac symptoms and were not initially suspected to have the COVID-19 disease. For example, in the report by Incardi et al. a 53-year-old woman presented with fatigue and hypotension with diffuse ST elevation and elevated troponins so coronary angiography was performed but negative. Given her symptoms and the current outbreak the team suspected myocarditis and their hypothesis was strengthened when she was found to be COVID-19 positive. Myocarditis was confirmed with cardiac MRI showing marked biventricular edema and gadolinium enhancement [39]. Similarly, in a series of four case reports by Fried et al. one of the patients had no symptoms other than chest pressure but was eventually found to be COVID-19 positive and again diagnosed with myocarditis [40].

More formal studies on the incidence of myocarditis have since been published as well. In a multicentered study of 84 patients, 13 (15.48%) were noted to have abnormal ECGs and cardiac enzyme levels, however only 4 (4.8%) were clinically diagnosed with myocarditis. The incidence of myocarditis in this study is lower than most other reports most likely due to confirmation of the diagnosis based on the clinical criteria for myocarditis mentioned previously [41]. Finally, in a case series by Chen et al. they reported increased levels of N-terminal pro B-type natriuretic peptide and cTnI in 27.5% and 10% of patients respectively. Interestingly, levels of IL-6 and other inflammatory cytokines were noted to be elevated especially in patients who experienced a more severe disease course requiring ICU admission. The group hypothesized that the elevated cytokines were due to cytokine storm, which they attributed as the cause of fulminant myocarditis in these patients [7]. In our next section, we will further discuss mechanisms that may result in myocardial injury secondary to infection with SARS-CoV-2.

4. Mechanisms of myocardial injury

The pathophysiological mechanisms underlying myocardial injury caused by COVID-19 are not well known so far and more studies need to be done to further delineate the mechanisms. As discussed previously, human SARS-CoV infection of the myocardium is known to be dependent on ACE-2 receptors. Disruption of ACE-2 leads to an age-dependent cardiomyopathy, cardiac dysfunction, and heart failure [42,43]. Oudit et al., hypothesized that the interaction between SARS-CoV and ACE-2 in the heart could contribute to SARS-mediated myocardial inflammation and damage. They reported that the SARS-CoV viral RNA was detected in autopsied human heart samples suggesting direct myocyte invasion of the virus. They further indicated marked down regulation of ACE-2 and reductions in ACE-2 protein in the heart samples. Moreover, they reported significant myocardial macrophage infiltration of post-mortem heart samples [13]. The detrimental effect of ACE-2 downregulation would impede cardioprotective effects of

angiotensin 1–7 leading to increased TNF α production [42,44]. TNF α is a common inflammatory cytokine and many researchers have shown that the inflammatory response may be at least partially responsible for the myocardial damage. For example, Guo et al. reported increased inflammatory marker, C-reactive protein, along with elevated TnT levels in patients with underlying CVD and poor outcomes, supporting the idea of severe inflammatory response as a possible mediator of cardiomyocyte damage [22].

In addition to TNF α , Zhao et al. discovered how SARS virus activates TGF- β signaling through the Smad pathway to induce lung fibrosis. This is also a common pathway of interstitial fibrosis development in the myocardium and could potentially be a mode of cardiac damage [45]. It has also been proposed that in patients with SARS, strong interferon-mediated responses could contribute to myocardial dysfunction. Specifically, in regard to interferons making the switch from hyperactive innate immunity to protective adaptive immunity [46,47]. Finally, another proposed mechanism is exaggerated cytokine response by Type 1 and 2 helper T cells [48].

Collectively, due to significant resemblance of SARS-CoV infection with COVID-19, the possible mechanisms of myocardial injury in COVID-19 could be direct damage to the cardiomyocytes, systemic inflammation, myocardial interstitial fibrosis, interferon mediated immune response, exaggerated cytokine response by Type 1 and 2 helper T cells, in addition to coronary plaque destabilization, and hypoxia.

5. Discussion

SARS-CoV-2, the cause of the COVID-19 disease, has emerged as a global health emergency, affecting almost every country in the world. Given the level of global interconnectivity, some epidemiologists have forecasted that 40–70% of the world's population will be infected with COVID-19 in the coming year [49]. If this is true, it means 40–70% of the population will experience anything from no symptoms at all, to mild respiratory symptoms, to severe and life-threatening respiratory symptoms. For the infected population, it appears underlying cardiovascular disease is related to worsening outcomes in patients who have COVID-19. In one study the case mortality rate more than tripled for patients with underlying cardiovascular disease [19]. This is not necessarily unique to coronavirus as many infections are made worse by underlying cardiac disease. However, it was also noted that patients with a history of cardiovascular disease were more likely to have elevated levels of cardiac enzymes such as TnT which suggests the possibility that these patients were more susceptible to cardiac injury via SARS-2-CoV [22]. As we are now investigating, it also appears that some of this cohort will experience extra-pulmonary manifestations of the virus including cardiovascular complications. Coronavirus affecting other organ systems is not new to this outbreak as it has been studied with SARS-CoV subfamily in general as well as MERS-CoV in the past. However, the reports of myocardial involvement related to COVID-19 so far seem to be increased when compared to previous SARS-CoV outbreaks. The most frequent manifestation cardiac involvement so far appears to be myocarditis. Of course, since clinicians are currently focusing on the most common and most lethal manifestations of SARS-CoV-2, we may see even more reports of cardiac complications as the pandemic progresses and other manifestations may become more prevalent. For now, research regarding cardiac manifestations has focused mostly on myocardial damage including myocarditis and, in some cases, fulminant myocarditis with cardiogenic shock. Several reports have already investigated the incidence of myocarditis in COVID-19 patients and some have reported circulatory failure resulting from myocardial damage secondary to the viral disease as the cause of death [36]. Interestingly, emerging case reports are also showing that patients are presenting without respiratory symptoms and instead with chest pain, pressure, fatigue, etc. and later being found to be COVID-19 positive with myocarditis. The mechanisms leading to cardiac damage are numerous and include direct insult to myocytes by the virus, cytokine

and interferon inflammatory responses, myocardial interstitial fibrotic response, T1 and T2 helper cell response [45–48]. What is known about the SARS-CoV subfamily in general is that they enter cells through ACE-2 receptors. Further research showed that ACE-2 receptors are expressed on lung alveolar epithelial cells, gastrointestinal epithelial cells, and endothelial cells of the arteries and veins. The latter expression suggests how the virus can cause direct insult to the heart [11,20].

Several key points have been gleaned through this review of myocardial injury as it relates to Covid-19. First, it appears that this strain of SARS-CoV has an increased propensity for developing extra-pulmonary complications, namely myocardial involvement. The reporting of myocardial involvement is likely still very low given the current focus on the more common respiratory symptoms. Second, it shows that while cardiac involvement is often self-limiting, some studies have reported myocardial injury as being the cause of death and thus it is important that clinicians have this complication on their radar [36]. Third, some case reports have accounts of patients who presented without respiratory symptoms and were later found to be COVID-positive after being diagnosed with myocarditis. With the emphasis of respiratory involvement of the COVID-19 syndrome, it is important to keep a high index of suspicion for the disease in patients presenting atypically to ensure we minimize community and healthcare worker exposure. Finally, our review found that there are many proposed mechanisms of myocardial damage secondary to COVID-19 infection, but more research is required to delineate whether the virus causes direct myocardial injury, inflammatory mediated injury, or injury through another mechanism.

6. Conclusions

COVID-19 infection has been associated with myocardial injury, which has been implicated with more severe disease courses and even death. Remarkable efforts are being done to elaborate underlying mechanisms of myocardial injury. Due to the acuteness of this pandemic, the scientific world currently lacks randomized controlled trials in order to fully elucidate the pathophysiological mechanisms and therapeutic measures. However, there are a handful of clinical trials on the way to assess possible therapeutic targets for the treatment and prevention of this disease. Even while lacking substantial evidence, certain conclusions can be drawn from this review. Namely, it appears extra-pulmonary manifestations are more likely with this SARS outbreak, and clinicians should maintain a high index of suspicion for COVID-19 infection even in patients without respiratory symptoms, as delayed testing will result in increased community and healthcare worker spread.

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Declaration of competing interest

None declared.

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