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Short communication

Cardiac injuries in coronavirus disease 2019 (COVID-19)

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ABSTRACT

As the coronavirus disease 2019 (COVID-19) epidemic worsens, this global pandemic is impacting more than 200 countries/regions and more than 4,500,000 confirmed cases worldwide. COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which might attack not only the respiratory system, but also the other important organs, including the heart. It was reported that COVID-19 patients with a past history of cardiovascular diseases would have a higher mortality. Meanwhile, elevated troponin levels were frequently observed in COVID-19 cases. Besides the comprehensive treatments for COVID-19, as a cardiologist, we should also remain vigilant about the cardiac injuries, especially those with severe emergent cardiovascular symptoms.

1. Introduction

On January 21th, 2020, the world health organization (WHO) released its first situation report about the outbreak pneumonia caused by a novel coronavirus in China commenced in Wuhan since last December [1]. Later, the etiology was isolated and identified as a new type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease was named as coronavirus disease 2019 (COVID-19) [2]. As the virus spread rapidly, the number of cases is rising at an exponential rate [3].

SARS-CoV-2 is the seventh coronavirus known to infect human, of which 3 coronavirus outbreaks had been reported in the 21st century. In 2003, SARS-CoV caused 8098 reported cases and 774 deaths (case fatality rate, 9.6%) in 37 countries before the epidemic was controlled [4]. Since 2012, Middle East respiratory syndrome coronavirus (MERS-CoV) has caused 2494 reported cases and 858 deaths (case fatality rate, 34%) in 27 countries [4]. Comparing with them, SARS-CoV-2 currently infected much more cases, with a case fatality rate about 7% as of the beginning of May 2020 (https://www.who.int/).

It was reported that SARS-CoV-2 used the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming [5]. Biopsy samples taken from COVID-19 patient showed bilateral diffuse alveolar damages with cellular fibromyxoid exudates [6]. Although SARS-CoV-2 mainly attacks the lungs, ACE2 is widely expressed in various organs, such as the heart and the liver. In addition, more and more SARS-CoV-2-related cardiac injury cases were reported. In this review, we will summarize the rapidly evolving discoveries in this field.

2. COVID-19 and cardiac injury

Cardiac injury, indicated by increased hypersensitive troponin I (hs-cTnI), is a common co-morbidity in COVID-19 patients, reported from 12 to 77% of cases. The clinical features of patients infected with SARS-CoV-2 were first described by Huang et al. [7]. Among the enrolled 41 hospitalized patients, 13 had underlying diseases, including diabetes (8, 20%), hypertension (6, 15%), and cardiovascular diseases (6, 15%). Common symptoms at the onset were fever, cough, and myalgia or fatigue. Finally, 13 (32%) patients were admitted to an intensive care unit (ICU) and 6 (15%) died. It should be noticed that acute cardiac injury was observed in 5 (12%) cases. Later, a retrospective cohort study conducted by the same group revealed the clinical course and risk factors for mortality of adult inpatients with COVID-19 [8]. Among the 191 enrolled patients, 137 were discharged and 54 died in hospital. About half of the patients (91, 48%) had a comorbidity, including hypertension (58, 30%), diabetes (36, 19%) and coronary heart disease (CHD) (15, 8%). In univariable analysis, odds of in-hospital death was much higher in patients with CHD or diabetes. Elevated hs-cTnI was also associated with death. In non-survivors, hs-cTnI increased rapidly from day 16 after disease onset, indicating that the cardiac injuries in COVID-19 might not progress linearly, but suddenly exacerbate. Recently, another retrospective cohort study with 113 deceased patients with COVID-19 also found that common complications observed more

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frequently in deceased patients were acute respiratory distress syndrome (ARDS) (113; 100%), type I respiratory failure (18/35; 51%), sepsis (113; 100%), acute cardiac injury (72/94; 77%) and heart failure (41/83; 49%) [9]. Patients with cardiovascular comorbidities were more likely to develop cardiac complications. Regardless of history of cardiovascular diseases, acute cardiac injury and heart failure were more common in deceased patients.

As cardiologists, our group focused on the cardiac injury in patients with COVID-19, and evaluated the correlation of serum N-terminal pro B-type natriuretic peptide (NT-proBNP) and hs-cTnI with the severity of COVID-19 [10]. Our data showed that prevalence of elevated NT-proBNP and hs-cTnI, hypertension and CHD were significantly higher in critical COVID-19 cases than in the mild COVID-19 cases. Moreover, elevated NT-proBNP, elevated hs-cTnI, elevated, hypertension, and CHD were significantly correlated with critical COVID-19 status. Most importantly, elevated cTnI (odds ratio [OR] = 26.909, 95% confidence interval [CI] 4.086–177.226, P = .001) and CHD (OR = 16.609, 95% CI 2.288–120.577, P = .005) were the independent risk factors of critical COVID-19 status. This was further confirmed by a pooled analysis of 8910 COVID-19 patients from 169 hospitals in Asia, Europe, and North America focusing on the effects of COVID-19 on cardiovascular system, which showed that CHD was independently associated with an increased risk of in-hospital death. Further, the association between increased hs-cTnI and unfavorable clinical outcomes was confirmed in 2 more cohorts [11,12].

3. Myocarditis in COVID-19

Lessons from the previous coronavirus and influenza epidemics suggest that viral infections can trigger various cardiovascular diseases [13]. Sporadic autopsy in COVID-19 cases suggested infiltration of myocardium by interstitial mononuclear inflammatory cells [6]. High amounts of T-helper-1 (Th1) cell response related cytokines, including interleukin 1β (IL-1β), interferon γ (IFN-γ), IFN-γ inducible protein 10 (IP-10), and monocyte chemotactic protein 1 (MCP-1) were detected in the plasma of COVID-19 patients, while T-helper-2 (Th2) cell response related cytokines, such as IL-4 and IL-10 were also increased [7]. Elevated plasma IL-6 was detected in COVID-19 patients with illness deterioration, and associated with death [8].

Considering the etiological characteristics and the high inflammatory burden, we speculate that myocarditis, especially fulminant myocarditis (FM) might be also induced by SARS-CoV-2 (Fig. 1A). Infection caused by various pathogens, especially virus, was the most common etiology of FM [14]. The cardiotropic virus, such as coxsachievirus B3 (CVB3) and parvovirus B19 (PVB19), could infect the heart directly, and the cardiac origin inflammation would lead to multiple organ dysfunction finally. The other non-cardiotropic virus, including SARS-CoV and influenza virus H1N1, might infect other types of host cells, and the inflammatory cells recruited from systemic inflammation to the heart would eventually damage the cardiac function. Autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatism could also induce FM. Another important etiology of FM is the recent increasing use of immune related therapeutic drugs, for example check-point inhibitors, chimeric antigen receptor T (CAR-T) cell immunotherapy, and multiple monoclonal antibodies, which could trigger both direct cardiac inflammation induced injury and indirect cardiac injury caused by systemic inflammation [15]. Various etiologies of FM might induce different contents of cytokine storm, which would finally cause cardiac dysfunction, even death (Fig. 1B).

The first SARS-CoV-2 FM case was reported by Hu et al. [16]. This 37-year-old male patient was diagnosed as SARS-CoV-2 FM with cardiogenic shock and pulmonary infection. The treatments included methylprednisolone to suppress inflammation (200 mg/day, 4 days), and immunoglobulin to regulate immune status (20 g/day, 4 days), norepinephrine to raise blood pressure, diuretic (toracemide and furosemide) to reduce cardiac load, milrinone to increase myocardial contractility, piperacillin sulbactam for anti-infection, pantoprazole, to inhibit gastric acid. One week later, the patient's symptoms improved significantly, markers of myocardial injury dropped, and X-ray chest film and echocardiography showed normal presentations. In line with the current Chinese experience, “Life support-based comprehensive treatment regimen”, early application of sufficient doses of immunemodulation drugs was adopted [17,18]. Meanwhile, the myocardial localization of SARS-CoV-2 was confirmed in an Italian COVID-19 patient with acute cardiogenic shock [19]. However, considering that SARS-CoV-2 could also infect endothelial cells [20], the effects of SARS-CoV-2 on different cell types in FM require further investigations.

The FM patients often present acute cardiac dysfunction or shock. It is difficult to distinguish the etiology of FM from clinical presentations. We summarized the differences among various etiologies induced FM in Table 1. According to the current reports, non-cardiotropic virus, such as SARS-CoV mainly induces lymphocytic myocarditis, while other etiologies induced FM could manifest various histologic subtypes. Because of the limited endomyocardial biopsy, further pathological investigations are needed to make a solid conclusion. Life support-based comprehensive treatments, including ECMO, ventilatory support and CRRT, are no doubt the core of FM therapy. Due to the different immune processes, immunomodulatory therapies should be administrated under individualized assessments. Meanwhile, the diverse cytokine patterns induced by different etiologies are also critical to apply the precise cytokine monoclonal antibody therapy. Clinical data showed that human interleukin-1 receptor antagonist, anakinra, might be beneficial in PVB19 induced FM. Recent study revealed that the tocilizumab could counteract the distinct increased IL-6 in COVID-19, which might be a potential treatment for SARS-CoV-2 induced FM.

FM in an individual is the net effect of the triggering cause (e.g. virus, microbial agent, the autoreactive process, checkpoint inhibitor therapy, adverse drug reactions) and host genetics and predisposition. Upon infection, the balance between pro- and anti-inflammatory cytokines would be disrupted, certain extent immune response will be benefit for eliminating pathogens. However, if pro-inflammatory cytokines are induced beyond control, the host itself will be damaged by the over-activated inflammation (Fig. 1C).

Previous data from various centers indicated that the inflammatory reactions during FM could not only cause severe injury to the myocardium [21], but also lead to the healing process. Biomarkers of necrosis (e.g. hs-cTnI), inflammation (e.g. C-reactive protein [CRP], lactic dehydrogenase [LDH], and soluble suppression of tumorigenicity [sST2]), and heart failure (e.g. NT-proBNP) were increased in FM patients. The interaction between innate and adaptive immunity with the respective effector organs and the response of key cytokines are respective markers of inflammation. The clinical results of these contributing factors ranged from functional recovery to death of cardiogenic shock. Interventions based on the timing and type of immune injury might improve the outcome. In patients with a virus positive endomyocardial biopsy interferon β and i.v. immunoglobulins including not only i.v. IgG but also i.v. IgG, M and A have been tested with positive success [22]. Considering the cytokines patterns in COVID-19 patients, certain cytokine antagonists and cytokine absorption might be also promising therapeutic strategies for rescuing SARS-CoV-2-associated immune dysregulation in COVID-19 patients with FM [23]. However, due to the limited case reports and registry trials, the efficacy of these immunomodulatory therapies in myocarditis associated with COVID-19 needs more evidence-based data.

4. Conclusion

With the rapid spread of COVID-19, cardiovascular comorbidities are common in patients with COVID-19 and such patients are at higher risk of morbidity and mortality. Due to the lack of echocardiography, angiography and magnetic resonance image (MRI), especially histopathological examination, the diagnosis of COVID-19 related

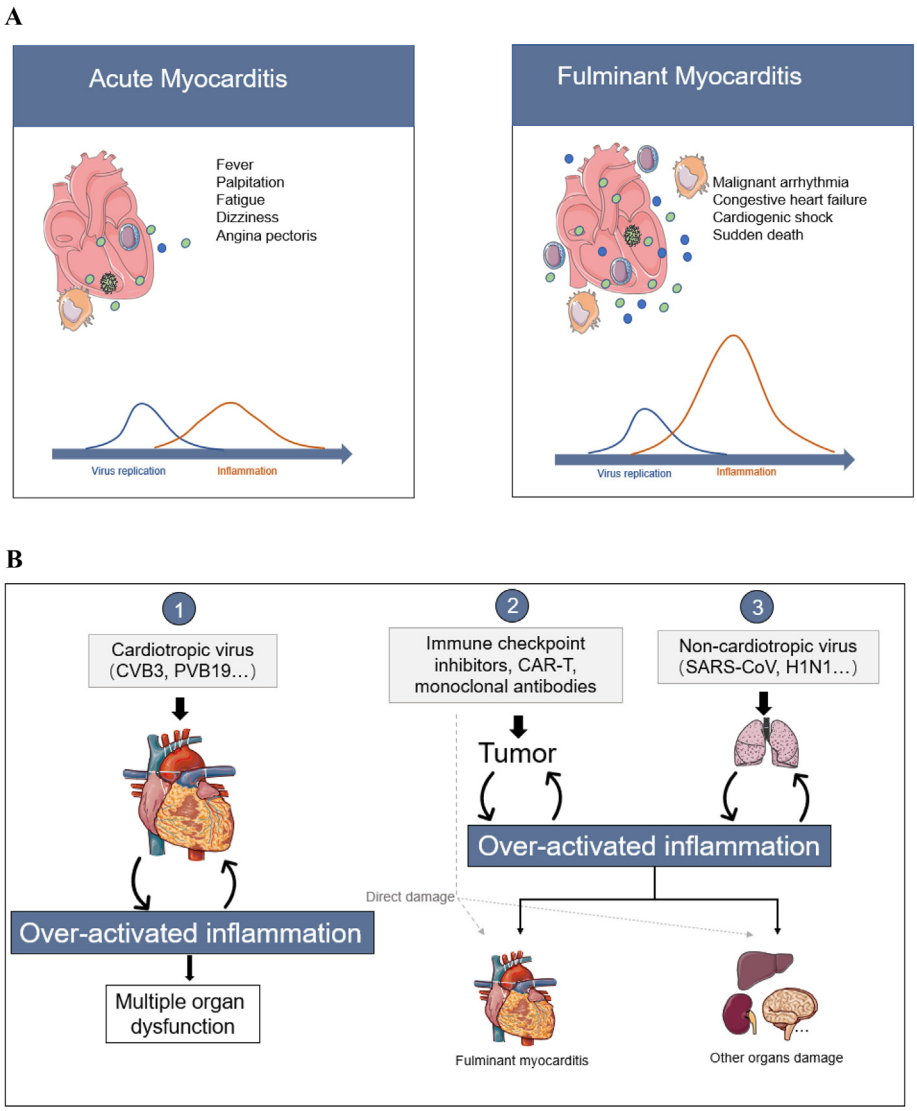

Fig. 1. (A) Different immunological mechanisms between acute myocarditis and FM. Myocarditis exhibits a broad spectrum of symptoms from mild chest pain to acute heart failure. The most significant clinical presentation of FM is the sudden onset of cardiac dysfunction. In acute myocarditis, the controllable immune response followed by virus replication could eliminate virus with minimal tissue damage and relatively mild cardiac symptoms. However, over-activated immune response could induce extremely magnified inflammation and rapid deterioration of cardiac function in FM. (B) The relationship between common etiologies of FM and over-activated inflammation. Over-activated inflammation plays a central role in the pathogenesis of FM: 1) cardiotropic virus directly invade cardiomyocytes, which induces heart tissue injury and inflammation. Over-activated inflammation could further promote heart damage and lead to multiple organs dysfunction. 2) In drugs induced FM, the combination of drugs and tumor could trigger inflammation. Increased circulating cytokines promote inflammatory infiltration in off-target organs, especially the heart. Besides, some of the drugs could directly attack cardiomyocytes, which further exacerbates cardiac function. 3) Non-cardiotropic virus attack its target organ (lung in the most cases) and trigger inflammation. Increased circulating cytokines then induce heart and the other organs damage through different ways. (C) Balance between pro-inflammatory and anti-inflammatory mechanisms during virus infection. Generally, the immune system could maintain a perfect balance through exquisite self-regulation between pro- and anti-inflammatory mechanisms. After infection, pro-inflammatory mechanisms are prevailed to facilitate pathogens clearance. Once the pathogens are eliminated, the anti-inflammatory mechanisms would calm down immune response and prevent over-activated immune response mediated damage. But under extreme conditions, the immune response is excessively activated, and the overwhelming pro-inflammatory response will induce cytokine storm.

Table 1
Comparations between SARS-CoV-2 and the other etiologies induced FM. SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, middle east respiratory syndrome coronavirus; CVB3, coxsackievirus B3; PVB19, parvovirus B19; ICIs, immune checkpoint inhibitors; CAR-T, chimeric antigen receptor modified T cell therapy; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; ECMO, extracorporeal membrane oxygenation; CRRT, continuous renal replacement therapy; IABP, intra-aortic balloon pump; IFN, interferon.

Etiology		Cardiac function	Histology	Cytokines	Treatments
Non- cardiotropic virus	SARS-CoV	Arrhythmia, myocardial infarction, cardiogenic shock, heart failure	Lymphocytic myocarditis	IL-2, IL-7, IL-10, G-CSF, IP10, MCP-1, MIP-1A, TNF-α	Ventilatory support, ECMO, CRRT, antiviral therapy, immunomodulatory therapy
	H1N1	Arrhythmia, atrioventricular block, congestive heart failure	Lymphocytic myocarditis	IL-8, IL-9, IL-17, IL-6, TNF-α, IL-12, p70, IL-15, IL-6	Ventilatory support, ECMO, antiviral therapy
	MERS-CoV	Arrhythmia, cardiogenic shock, heart failure	Lymphocytic myocarditis	IFN-γ, TNF-α, IL-15, IL-17	Ventilatory support
Cardiotropic virus	CVB3	Arrhythmia, atrioventricular block, myocardial infarction, cardiogenic shock, congestive heart failure	Lymphocytic (mainly), eosinophilic and giant-cell myocarditis	IL-1β, IL-2, IL-6, TNF-α, IL-1Ra, sTNFR-1, IL-10, IFNs, IL-4, IL-17B	Circulatory support (ECMO, IABP, Impella), CRRT, IFN, immunomodulation therapy, antiviral therapy, anakinra
	PVB19	Arrhythmia, atrioventricular block, myocardial infarction, cardiogenic shock, congestive heart failure	Lymphocytic (mainly), eosinophilic and giant-cell myocarditis, cardiac sarcoidosis	IL-6, IL-8, TNF-α, IFN-γ	Circulatory support (ECMO, IABP, Impella), CRRT, immunomodulation therapy, antiviral therapy, anakinra
Drugs	ICIs, CAR-T	Arrhythmia, myocardial infarction, cardiogenic shock, congestive heart failure	Lymphocytic, eosinophilic and giant cell (rare) myocarditis	IFN-γ, TNF-α, IL-6, IL-1, IL-10, IL-8, IL-2, GM-CSF	Immunomodulatory therapy, supportive care
Autoimmune diseases	SLE, RA	Atrioventricular block, heart failure	Lymphocytic, eosinophilic and giant cell myocarditis	Not reported	Immunomodulation therapy

cardiovascular damage is still not clear. Cohorts of larger sample sizes are required to illustrate the roles of COVID-19 in cardiac injury, especially FM. While the life-support treatments might be helpful in treating COVID-19 patients with multiple organ dysfunction, the immunomodulatory therapies to COVID-19 patients with both high load of inflammation and cardiovascular injury should be administrated under careful individualized assessments.

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Not applicable.

Code availability

Not applicable.

Declaration of Competing Interest

The authors have declared that no competing interests exist.

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