The Heart Surgery Forum #2020-2959
23 (4), 2020 [Epub June 2020]
doi: 10.1532/hsf.2959

Online address: http://journal.hsforum.com

Progress in Treatment of Myocardial Injury in Patients with 2019-nCoV: A Chinese Experience

Shixiong Wei, Huimin Cui, Lin Zhang, Shengli Jiang

Department of Cardiovascular Surgery, Chinese PLA General Hospital, Beijing, China

ABSTRACT

Since December 2019, the 2019 novel coronavirus (2019-nCoV) infection began to appear in Hubei Province of China and gradually spread to other provinces and other countries. The virus has the characteristics of strong transmission capacity, diverse clinical manifestations, long incubation period, and latent infection, thus posing a serious threat to human life safety and health. With the increasing number of cases and the continuous enrichment of clinical data, 2019-nCoV–infected patients have received more and more attention regarding myocardial injury related to virus infection besides typical respiratory system manifestations. According to the published data, we summarize the myocardial injury manifestations, characteristics, effects on disease condition, and prognosis of 2019-nCoV–infected patients and discuss the possible injury mechanism, treatment methods, and future research directions.

INTRODUCTION

AIn December 2019, a newly discovered coronavirus, 2019 novel coronavirus (2019-nCoV), was isolated and identified from respiratory epithelial cells of patients with unexplained pneumonia in Hubei Province of China. The disease caused by the virus infection is novel coronavirus (COVID-19). COVID-19 broke out in Wuhan and spread to the whole province and other provinces and countries, posing a serious threat to human life safety and health. More than 2 million infections have been confirmed worldwide, resulting in more than 400,000 deaths.

nCoV belongs to the order of nested viruses, coronaviridae, and the genus of coronaviruses B. It is a class of enveloped nonsegmented single-stranded positive strand RNA viruses with a diameter of 50~200 nm [Peng 2020] and is the seventh member of the genus of coronaviruses found so far that can infect humans. Among the other 6 coronaviruses that have been confirmed to infect human beings, 4 (229E, OC43, NL63, and HKU1) are widespread but cause only common upper respiratory tract infection symptoms, and the other 2 are severe acute respiratory syndrome (SARS) coronaviruses, SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which can both cause fatal diseases [WHO 2020]. Whole-genome sequencing results show that the sequence consistency of 2019-nCoV genome and SARS-CoV genome is 79.5%, and the virus is considered to be a coronavirus related to SARS-CoV [Ashour 2020].

The pathway of 2019-nCoV entering the host cell is the same as SARS-CoV, ie, through angiotensin converting enzyme 2 (ACE2). Current statistical data show that 2019-nCoV may not be as lethal as SARS-CoV and MERS-CoV. An epidemiological survey that included 44,672 confirmed cases showed that the crude fatality rate after 2019-nCoV infection was 2.3%, and the fatality rate density was 0.015/10 person days. However, the rapid increase in the number of cases and clear evidence of interpersonal transmission show that the virus is more infectious than SARS-CoV and MERS-CoV [Jin 2020]. The frozen electron microscope test results of 2019-nCoV show that its affinity with ACE2 is 10 to 20 times higher than that of SARS-CoV, which also indicates that the virus is highly infectious [Cao 2020].

2019-nCoV infection mainly involves the respiratory tract, and its clinical first manifestations are fever, dry cough, fatigue, and wheezing. Severe cases may develop to severe pneumonia, acute respiratory distress syndrome, and systemic multiple organ dysfunction [Fan 2020]. It is worth noting that more and more case data show that 2019-nCoV infection not only causes typical respiratory symptoms, but also affects the cardiovascular system, including serious myocardial damage, thus aggravating the disease condition and affecting the prognosis. Based on the research results published so far, we discuss the manifestations, characteristics, laws, and effects on prognosis of myocardial injury caused by 2019-nCoV infection.

MYOCARDIAL INJURY IN COVID-19

Myocardial Injury Is Widespread in Patients Diagnosed with COVID-19

Irrespective of the presence or absence of basic cardiovascular diseases, abnormal elevation of myocardial injury markers widely exists in patients diagnosed with COVID-19 and is closely related to disease progression and prognosis. Among the 41 patients diagnosed as COVID-19 published by Fan et al [2020], 5 (12%) were definitely diagnosed with acute myocardial injury associated with 2019-nCoV infection, mainly manifested as high-sensitivity cardiac troponin I (hs-cTnI) level

Received March 12, 2020; accepted March 18, 2020.

Correspondence: Shengli Jiang, PhD, Department of Cardiovascular Surgery, Chinese PLA General Hospital, Beijing, China; 86 13269330000 (E-mail: jiang_shengli301@163.com.

rising (≥ 28 ng/L). One of them was a mild case, accounting for 4% of the total number of mild cases. Four patients were admitted to intensive-care unit (ICU), accounting for 31% of the total number of severe patients. In the retrospective study published, which included 99 confirmed patients with COVID-19, most patients had elevated myocardial injury markers, specifically, increased creatine kinase (CK ≥ 310 U/L) in 13% of patients and increased lactate dehydrogenase (LDH ≥ 250 U/L) in 76% of patients. In another single-center retrospective study involving 138 confirmed patients with COVID-19 [Jin 2020], 10 patients (7.2%) were diagnosed with acute myocardial injury, of which 2 were mild cases, accounting for 2% of the total number of mild cases. Eight cases were severe patients admitted to the ICU, accounting for 22% of the total number of severe patients. Moreover, compared with mild patients, the creatine kinase isoenzyme CK-MB, LDH, and hs-cTnI of severe patients admitted to ICU are higher, proving that 2019-nCoV infected myocardial damage is related to the progression of the disease. Among the earliest published deaths, one confirmed patient was admitted with severe 2019-nCoV infection–related myocarditis as the main manifestation, with myocardial injury markers as high as 20 times the normal upper limit, and corresponding electrocardiographic abnormalities [Peng 2020].

The first multicenter retrospective study included 1,099 confirmed patients with COVID-19 from 552 hospitals in 31 provinces in China [Yang 2020]. According to the guidelines for adult community-acquired pneumonia issued by the American Chest Association, the study classifies patients with COVID-19 into severe and nonsevere types. The main composite endpoint events include ICU admission, mechanical ventilation, and death. The results showed that the expression level of myocardial injury markers was higher in severe patients and patients with major composite endpoint events. Among 675 patients with LDH data, 277 (41%) had LDH elevation (≥250 U/L), accounting for 37.2% of nonsevere patients and 58.1% of severe patients. LDH elevation occurred in 70.5% of patients with major composite endpoint events, but only 39.0% of patients without major composite endpoint events. Among 657 patients with CK data, 90 patients (13.7%) had CK elevation (≥200 U/L); compared with patients without major composite endpoint events, patients with major composite endpoint events had a higher proportion of CK elevation (26.1% versus 12.8%, P = .021). The above study also confirmed that myocardial injury is closely related to the severity of the disease and even the prognosis in patients with COVID-19. In addition, in a case of familial aggregation in Shenzhen, LDH increased (≥214 U/L) in 3 of the 5 confirmed patients with COVID-19, and the 3 patients were all >60 years old, with more severe symptoms after onset [Fan 2020]. The first confirmed case of COVID-19 reported in the United States also had a full rise in LDH during hospitalization [Chen 2020].

Atypical Clinical Manifestations Suggest the Possibility of Myocardial Injury

The most common clinical symptoms of patients with COVID-19 are fever (87.9%) and cough (67.7%), and other common manifestations include fatigue (38.1%) and cough-up phlegm (33.4%) [Liu 2020b]. However, with the increasing number of confirmed cases, it is not uncommon to encounter a patient with COVID-19 whose first symptom is cardiovascular. Of the 99 confirmed cases of COVID-19 reported by Chen et al [2020], 2 (2%) showed chest pain on admission. However, in a multicenter retrospective study in Hubei province that included 137 confirmed patients with COVID-19, 10 patients (7.3%) showed palpitations as the first symptom [Cascella 2020]. According to clinical observation, patients with COVID-19 with myocardial injury often show sinus tachycardia, especially nocturnal tachycardia, and the acceleration of heart rate is not commensurate with the increase of body temperature (≥10 times/°) [Jin 2020]. These atypical clinical manifestations of cardiovascular diseases suggest the possibility of viral infection involving the myocardium. Of course, the possibility of pleural involvement or fever causing the above symptoms needs to be ruled out, and whether the myocardial injury being related to 2019-nCoV infection can be clearly diagnosed needs further verification.

Mechanisms of Myocardial Injury Associated with 2019-nCoV Infection

The pathogenesis of 2019-nCoV infection-related acute myocardial injury is still unclear, and the following three mechanisms may play an important role.

First, 2019-nCoV directly infects and invades myocardial cells, causing myocardial cell damage and viral myocarditis. 2019-nCoV invades human cells through high-affinity binding of S protein with ACE2, which is highly expressed in myocardial tissue and plays an important role in the cardiovascular system [Liu 2020a]. Although myocardial injury markers and electrocardiographic abnormalities in some patients highly suggest that 2019-nCoV directly infects myocardium and leads to myocarditis, and SARS-CoV and MERS-CoV both have reports of myocarditis [Liu 2020b], more exact pathological and imaging evidence is still needed to confirm.

Second, hypoxemia, respiratory failure, shock, or hypotension induced by pulmonary infection lead to insufficient oxygen supply to the myocardium. After infection, the body metabolism is vigorous, the heart burden increases, and the imbalance of oxygen supply and demand causes myocardial damage, especially for patients suffering from chronic cardiovascular diseases such as coronary heart disease and heart failure.

Third, immune response disorders (cytokine storms) may also lead to myocardial damage. Previous studies have confirmed that cytokine storms play a crucial role in the pathogenesis of SARS-CoV and MERS-CoV, and may be related to cardiovascular system complications related to SARS-CoV infection [Liu 2020b]. Chen et al [2020] found that during 2019-nCoV infection, the increase of proinflammatory factors such as interleukin (IL)-1β, interferon-γ, interferon-inducible protein 10, and monocyte chemoattractant protein 1 may lead to the activation of helper T lymphocyte 1 (adaptive T helper 1, or Th1) [Yang 2020]. Moreover, compared

with mild COVID-19 patients, the concentrations of granulocyte colony-stimulating factor, interferon-inducible protein 10, monocyte chemotactic protein, and tumor necrosis factor-α in the plasma of severe patients are higher, suggesting that cytokine storms are closely related to the severity of the disease. A study that included 123 confirmed patients with COVID-19 found that compared with mild cases, severe cases had higher plasma concentrations of IL-6 and IL-10 and lower CD4+ T and CD8+ T cells [Ling 2020]. Another study that included 40 patients with COVID-19 also reached the same conclusion [Huang 2020]. However, cytokines related to helper T lymphocyte 2 (adaptive T helper 2, or Th2) that can reduce inflammatory response, such as IL-4, have also increased [Yang 2020], which is the feedback regulation of the body on excessive inflammatory response or other effects, yet to be revealed by further research. In a word, 2019-nCoV infection may lead to imbalance of Th1 and Th2 cells. The cytokine storm caused by 2019-NCOV infection may be one of the important mechanisms of myocardial injury, and may also be an important mechanism of multiple organ failure caused by immune imbalance.

TREATMENT AND PROSPECTS

At present, the exact mechanism of myocardial damage caused by 2019-nCoV infection is not completely clear, but through the above basic and clinical studies, it can be clearly confirmed that 2019-nCoV infection can cause myocardial damage that is closely related to the progression and prognosis of the disease.

In terms of treatment, first of all, we should actively treat 2019-nCoV infection to control the progression of pneumonia. If patients have cardiovascular diseases at the same time, they should also be actively controlled and treated. The American College of Cardiology issued a notice on the impact of COVID-19 on the heart, suggesting that patients with COVID-19 complicated with cardiovascular diseases should be actively treated with statins, beta blockers, ACE inhibitors, aspirin, and other drugs to protect cardiovascular diseases as appropriate, and that priority should be given to infected patients complicated with chronic cardiovascular diseases [Cascella 2020]. Second, if acute myocardial injury occurs during the course of COVID-19, myocardial protection and nutrition drugs should be reasonably applied, such as coenzyme Q10 synthesized by increasing adenosine triphosphate, creatine phosphate sodium, vitamin C, polar solution, deep sea fish oil, etc. Third, if cardiac muscle injury leads to arrhythmia, corresponding treatment should be carried out according to arrhythmia types and combined with the hemodynamic status of patients. Once there are signs of heart pump failure, life support treatment such as extracorporeal membrane oxygenation should also be given as soon as possible.

The most important thing is to strengthen the awareness and vigilance of myocardial damage caused by 2019-nCoV infection, and to strengthen the monitoring of cardiac function and myocardial damage. In addition to chest tightness and chest pain, myocardial injury usually starts with shortness of breath and dyspnea, which may be masked by symptoms of pulmonary infection. Attention should be paid to it, and careful identification should be made.

In terms of diagnosis, according to the diagnostic criteria proposed by "experts from China's National Center for Geriatrics" [Jin 2020] patients suspected or confirmed of COVID-19 have myocardial injury markers (cTNI/cTNT) increased above the 99th percentile limit, and COVID-19–related myocardial injury can be diagnosed after acute coronary syndrome is excluded. In addition, the dynamic changes of myocardial injury markers are also the main reference standard for judging whether patients have myocardial injury in most clinical research of COVID-19. However, the level of myocardial injury markers is affected by infection, hypoxia, renal function, and other factors, and there may be false positives in patients with COVID-19. Therefore, it is not absolutely reliable to judge whether there is myocardial injury or myocarditis solely by myocardial injury markers. It is necessary to comprehensively judge whether there is myocardial injury or myocarditis according to the actual clinical situation of patients combined with the auxiliary examination results of electrocardiography, imaging, pathology, and other modalities. However, no publicly released imaging data such as echocardiogram and cardiac nuclear magnetic resonance of patients with COVID-19 have been seen so far.

At present, there are few research data on myocardial injury caused by 2019-nCoV infection, and there is a lack of pathological data of patients with myocardial injury. The pathological anatomy of the first death confirmed from COVID-19 showed that the myocardial tissue of the patient showed only a small amount of inflammatory infiltration of myocardial interstitial mononuclear cells, and no substantial myocardial damage was found. However, because that patient had no clinical manifestations of myocardial injury during the whole course of onset, based on the pathological results, it cannot be concluded that 2019-nCoV infection does not affect the myocardium.

In the future, pathological examination of myocardial tissue of patients with COVID-19 complicated with definite myocardial injury is needed to provide evidence of etiology for the study of myocardial injury. It is expected that there will be more targeted research on the mechanism, manifestations, laws, susceptible factors, outcomes, and prognosis of myocardial injury of COVID-19, so as to promote and continuously improve targeted treatment programs and improve the prognosis of patients.

ACKNOWLEDGMENTS

Dr. Shixiong Wei and Dr. Huimin Cui contributed equally to this article.

REFERENCES

Ashour HM, Elkhatib WF, Rahman MM, et al. 2020. Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. Pathogens 9:186.

Cao Y, Li L, Feng Z, et al. 2020. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discov 6:11.

Cascella M, Rajnik M, Cuomo A, et al. 2020. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls. Treasure Island, FL: StatPearls Publishing.

Chen L, Liu HG, Liu W, et al. 2020. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 43:E005.

Fan HH, Wang LQ, Liu WL, et al. 2020. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus (2019-nCoV) related coronavirus model. Chin Med J (Engl) 133:1051-1056.

Jin Y, Cai L, Cheng Z, et al. 2020. Novel coronavirus (2019-nCoV) guidelines for rapid diagnosis and treatment of pneumonia infected. PLA Med J 45:1-20.

Ling Y, Xu SB, Lin YX, et al. 2020. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl) 133:1039-1043.

Liu J, Zheng X, Tong Q, et al. 2020. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol doi: 10.1002/jmv.25709.

Liu Z, Xiao X, Wei X, et al. 2020. Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J Med Virol 5:491-494.

Peng W, Gan X, Tan Y, et al. 2020. Mechanisms of cardiovascular system damage and treatment progress of infectious diseases in novel coronavirus [J/OL]. Chin J Nosocomiol.

Peng YD, Meng K, Guan HQ, et al. 2020. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi. 48:E004.

WHO. 2020. Novel coronavirus-China [EB/OL]. http://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/.

Yang W, Cao Q, Qin L, et al. 2020. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 382:1708-1720.