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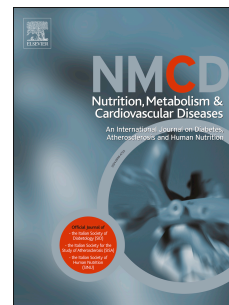
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A close-up on COVID-19 and cardiovascular diseases

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Abstract

Aims: To analyze the potential mechanism of cardiovascular dysfunctions induced by Coronavirus Disease 2019 (COVID-19) and to evaluate more effective therapeutic pathways for patients with cardiovascular diseases.

Data Synthesis: COVID-19 mainly invades the lungs, causing its serious damage. Studies found that COVID-19 induced the renin-angiotensin system imbalance, inflammatory storm, hypoxemia and stress response et al, all contributed to hypertension and serious myocardial damage in the process of virus pathogenesis, even increasing mortality in COVID-19 patients.

Conclusions: In the process of management of COVID-19 infections, close attention should be paid on both lung and cardiovascular damage, especially on those with only symptoms of cardiovascular diseases. Early identification, timely and effective treatments, maintenance of hemodynamics and electrophysiological stability are of great significance on effective treatment and long-term prognosis.

The pandemic of COVID-19 has been taking lives worldwide. It caused by a novel coronavirus which human being are lack of defensive function in whole population. It targets human's lung and causes serious damage of lungs. Based on early reports, for people with underlying heart issues, the concerns are serious. It appears people over 65 with coronary heart diseases or hypertension is more likely to be infected and to develop more severe symptoms. In addition, some of hospitalized COVID-19 patients had cardiovascular diseases in China. As characteristic analysis of COVID-19 patients, hypertension and severe myocardial damage contribute to severity [1] and mortality of COVID-19 patients [2]. Therefore, to better understand the development of COVID-19 and the impacts of cardiovascular diseases will add valuable measures to the management of COVID-19 patients.

1 Overview of COVID-19

The coronavirus is a kind of positive-chain single-stranded RNA virus with a diameter of 80~120 nm, which can be classified as α, β, δ, γ type. Coronavirus has the characteristics of various strains, wide distribution and cross species. The COVID-19 belongs to the β genus and has a capsule on which mushroom-like protein spike make the virus crown-like, round or oval size, and are often pleomorphic and with a diameter of 60-140 nm. Detection of viral genes showed that the nucleotide sequences of COVID-19 genome share 86.9% identity with severe acute respiratory syndrome virus (SARS-CoV) genome [3]. Current studies have shown that the COVID-19

transmission route is bat-human, and intermediate host is to be studied; it was transmitted by mainly respiratory droplets, as well as transmitted through contact during human-human transmission [4].

2 Potential mechanism of cardiovascular diseases induced by COVID-19

2.1 Imbalance of renin-angiotensin system

It has been confirmed that a portion of the region at the amino terminal of SARS-CoV spike protein could bind to human angiotensin-converting enzyme 2(ACE2) to mediate the fusion of virus and host cell [4]. COVID-19 are likely to have similar infection pathways to SARS-CoV, in other words, ACE2 may also be the binding receptor of COVID-19. ACE2 are homologous enzymes of angiotensin-converting enzyme (ACE), both of which are important components of the renin-angiotensin system (RAS).

Renin hydrolyzes angiotensinogen to angiotensin I (Ang I), that then is converted to angiotensin II (Ang II) by ACE. The Ang II leads to vasoconstriction, elevated blood pressure and vascular remodeling by binding to angiotensin type II 1 receptor (AT1R). ACE2 can act on Ang I and generate Ang (1-9), then they can generate Ang (1-7) through dependent or independent ACE2 pathways, or ACE2 can directly hydrolyze Ang II to Ang (1-7), in which Ang (1-7) can bind to G protein-coupled Mas receptors to mediate vasodilation, antioxidant stress; inhibit cell proliferation; protect vascular endothelium damage as well as other physiological functions, like delaying or reversing vascular remodeling and protecting the cardiovascular system. ACE/Ang

II/AT1R axis and ACE2/Ang (1-7)/Mas axis antagonize and balance each other to maintain the dynamic balance of human vascular system. ACE2 is expressed in human alveolar epithelial cells, and I which is not only the gateway of virus invasion, but also mediates lung injury and lung failure caused by virus infection. Clinical observations showed that plasma Ang II levels increased significantly in COVID-19 patients [5], which further suggests that COVID-19 binding to ACE2 leads to excessive release of Ang II through RAS, which in turn burdens heart and vascular system, by increasing heart loading, eventually cardiomyocyte hypertrophy and high blood pressure.

2.2 Inflammatory storm

Virus replicates in cells after its fusion with host cells, the invasion of lung surface cells directly causes lung inflammation; and the invasion of cardiomyocytes will lead to edema, degeneration and necrosis of cardiomyocytes. Meanwhile pro-inflammatory cytokines are released following cell lysis, such as interleukin (IL)1-6, endothelial adhesion factor, tumor necrosis factor, granulocyte colony stimulating factor, interferon, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α et al [6]. The accumulations of cytokines as well as the filtration of inflammatory cell from blood at the injury site, result in 'inflammatory storms', stimulating the overactivation of body immune response, increasing the damage or apoptosis of myocardial cells, decreasing the stability of coronary atherosclerotic plaques. All contribute to the increasing the risk of cardiovascular

events [6, 7].

2.3 Hyoxemia

The lung injury caused by COVID-19 leads to hyoxemia, the partial pressure of circulating oxygen and oxygen saturation decrease continuously, which lead to the accumulation of oxygen free radicals, lactic acid and other metabolites. Again，by circulating around whole body, myocardial cell injury becomes inevitable.

In order to ensure the supply of systemic cell metabolic energy demand, the heart pump blood is intensified, and prone to cardiac dysfunction and heart failure. In addition, hypoxemia is also one of the inducing factors of inflammatory response, which can promote the formation of inflammatory storm to a certain extent [8].

2.4 Stress response

The first and most strong reaction of virus invasion is the activation the human immune and inflammatory responses. The interactions among tissues, organs and pathogens are a complex stress process, especially severe infection. At the same time, the emotional response of human like anxiety, fear et al also increases the stress of patients. In the process, catecholamine is released in large quantities, and plasma catecholamine content is related to blood pressure level, blood perfusion, coronary heart disease and sudden cardiac death. High catecholamine has direct myocardial toxicity, which can lead to microcirculation disturbance, vasospasm and arrhythmia [9].

3 Clinical indications between COVID-19 with cardiovascular disease

3.1 Acute myocardial injury

The first most important clinical observations pointed to that a few patients infected with COVID-19 might have no sign of respiratory symptoms. Patients complained with palpitation, chest tightness, shortness of breath after exercises et al. As soon as such patients were confirmed or suspected as COVID-19, a sudden acute myocardial infarction, or heart failure will occur immediately. It is so important to early identify those patients with acquired quarantine measures.

When COVID-19 patients show increased respiratory rate, lower blood pressure and even shock, Electrocardiogram (ECG) with prolonged QRS interval, sychnosphygmia and frequent premature beats, abnormal increases in creatine kinase isoenzyme (CK-MB) and troponin measured by laboratory tests, or decreased left ventricular ejection fraction (LVEF) and decreased diffuse wall motion indicated by cardiac ultrasound during their hospitalization, we should beware of COVID-19 infection might involve the heart and have the possibility of fulminant myocarditis [10]. COVID-19 patients who may or have been confirmed with fulminant myocarditis need active life support treatment, including mechanical ventilation, intra-aortic balloon counterpulsation (IABP), extracorporeal membrane pulmonary oxygenation (ECMO), temporary pacemaker implantation, in addition to general treatment such as bed rest, nutritional support, protecting myocardial and reducing cardiac load. Meanwhile vital signs and hemodynamic indicators such as secondary

malignant arrhythmia, heart failure and other critical conditions should be closely monitored and treated in a timely manner. For acute myocardial injury caused by COVID-19, there are no specific therapeutic drugs [8-10].

3.2 Management of hypertensive patients

The clinical characteristics of COVID-19 patients showed that hypertension was closely related with the severity of COVID-19 infection; 20%-30% in in- patients, 58.3% in the intensive care unit (ICU) patients, and 60.9% in the death cases. It has been known that COVID-19 infects human by combining the spike protein on its surface with the ACE2 on the alveolar cell membrane, which in turn activates the immune system and releases cytokines and inflammatory factors. ACE2 is an important protective protein in human body; COVID-19 infection causes down-regulation of ACE2 level in the body, but has no obvious effect on ACE [9, 10].

The angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor antagonist (ARB) is associated with RAS regulation. Animal studies have shown that ACEI/ARB drugs can significantly increase the expression level and ACE2 biological activity in rat cardiomyocytes [11, 12]. It is unclear whether ACEI/ARB application will up-regulate the expression and activity of ACE2 in lung tissue. Therefore, there is no evidence that ACEI/ARB increases susceptibility to COVID-19 or lung damage following infection.

High blood pressure patients who are currently receiving ACEI/ARB treatment or other antihypertensive drugs are advised not to change the treatment plan without

clear contraindications or serious adverse reactions, so as not to affect blood pressure homeostasis and increase the risk of hypertension emergencies. Patients with both hypertension and COVID-19, their treatments with ACEI/ARB depend on their conditions. For patients with mild illness who have been given long-term medication of ACEI/ARB, they may have to continue it, while for those who have severe or critical illness; the treatment plan should be decided after careful monitoring of vital signs, hemodynamics and damage to target organs. To avoid dry cough caused by ACEI, COVID-19 infection patients are recommended that the use of the ACEI should be delayed.

3.3 Other cardiovascular conditions

The American Heart Society (ACC) published a clinical bulletin *Cardiac Implications of Novel Wuhan Coronavirus (COVID-19)*, and stated that COVID-19 has potential effects on the heart, especially in patients with cardiovascular disease. Among COVID-19 patients, there were about 50% diagnosed with chronic diseases, 40% with cardiovascular and cerebrovascular diseases, and patients with chronic or potential diseases, such as obesity, hypertension, diabetes, chronic obstructive pulmonary disease and chronic kidney disease, have a higher risk of complications or death after infection. Virus infection can destroy the stability of atherosclerotic plaque and promote the occurrence of coronary atherosclerosis and coronary heart disease. Some experts suggest that, during the outbreak, people with previous cardiovascular diseases should strictly accept tailored and optimized drug treatments to provide

additional protection, including statins, β receptor blockers, ACEI drugs and aspirin, in accordance with doctor's advice and guidance [12].

People with basic cardiovascular disease are more likely to be infected with the virus and with poor prognosis, and the virus infection can also lead to the deterioration of basic heart disease. COVID-19 patients who have been complicated with cardiovascular basic diseases, are recommended to give priority to treatment, meanwhile pay attention to vigilance against the recurrence or aggravation of the original basic diseases [8-10].

4 Summary

Above all, although the pathogenic mechanism of COVID-19 has not been fully elucidated, ACE2 is currently found to be a key molecular target for COVID-19 occurrence and progression, and the heart and lung tissues are both important target organs for COVID-19. The hypoxemia, respiratory distress, inflammatory storms caused by COVID-19 have adverse effects on the heart, and we should pay more attention to the cardiovascular damage induced by COVID-19. Early identification, timely and effective treatment, maintenance of hemodynamics and electrophysiological stability are of great significance to alleviate the disease, save lives, and ensure long-term prognosis.

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Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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