

# Role of Neuroimmune Interactions in COVID-19-related Cardiovascular Damage\*

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**[Abstract]** Coronavirus disease 2019 (COVID-19) has caused a global pandemic impacting over 200 countries/regions and more than 200 million patients worldwide. Among the infected patients, there is a high prevalence of COVID-19-related cardiovascular injuries. However, the specific mechanisms linking cardiovascular damage and COVID-19 remain unclear. The COVID-19 pandemic also has exacerbated the mental health burden of humans. Considering the close association between neuroimmune interactions and cardiovascular disease, this review assessed the complex pathophysiological mechanisms connecting neuroimmune interactions and cardiovascular disease. It was revealed that the mental health burden might be a pivotal accomplice causing COVID-19-associated cardiovascular damage. Specifically, the proinflammatory status of patients with a terrible mood state is closely related to overdrive of the hypothalamus-pituitary-adrenal (HPA) axis, sympathovagal imbalance, and endothelial dysfunction, which lead to an increased risk of developing cardiovascular injury during COVID-19. Therefore, during the prevention and treatment of cardiovascular complications in COVID-19 patients, particular attention should be given to relieve the mental health burden of these patients.

**Key words:** neuroimmune interactions; COVID-19; mental health burden; autonomic nervous system; endothelial dysfunction.

Coronavirus disease 2019 (COVID-19) has spread globally to infect over 200 million individuals and has killed more than 4 million people in over 200 countries/regions as of August 12, 2021. Worldwide, human health and the economy have been drastically impacted on an unprecedented scale. Although the clinical manifestations of COVID-19 primarily include respiratory symptoms, many patients experience cardiovascular damage, including acute cardiac injury and brain medullary cardiorespiratory dysfunction<sup>[1-3]</sup>. One explanation is that angiotensin-converting enzyme 2 (ACE2), as the receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is widely expressed in the lungs, brain, and cardiovascular system<sup>[4-7]</sup>. Although the specific causes of COVID-19-related cardiovascular damage in patients remain

unclear, a cytokine storm triggered via an imbalanced response to pro- or anti-inflammation may play a vital role<sup>[8-11]</sup>. Furthermore, COVID-19 has exacerbated the mental health burden of people throughout the world as they experience stress and depression due to the pandemic<sup>[12, 13]</sup>. In turn, a severe mental health burden may make COVID-19-related cardiovascular disease (CVD) worse<sup>[14-16]</sup>. Therefore, elucidating the potential direct and associated pathophysiological mechanisms leading to SARS-CoV-2-related CVD concerning the immune system and the mental health burden of infected patients will help us better understand COVID-19.

## 1 IMPACTS OF COVID-19 ON CARDIOVASCULAR SYSTEM

Accumulated evidence indicates that patients with SARS-CoV-2 infection can develop cardiovascular complications, such as congestive heart failure, acute myocarditis, pericarditis, cardiac arrhythmias, and vasculitis. In addition, approximately 8%–28% of COVID-19 patients exhibit cardiac injury with troponin release early in the disease process.

In Wuhan, Huang *et al* reported that myocardial injury associated with COVID-19 existed in 5 of the

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first 41 patients; moreover, four of five myocardial-injury-related patients infected with COVID-19 who were admitted to the intensive care unit (ICU) presented with severe cardiac damage<sup>[8]</sup>. Meanwhile, Wang *et al* reported that 36 patients treated in the ICU had significantly elevated levels of myocardial-injury biomarkers, such as creatine kinase-MB and high-sensitivity troponin I<sup>[17]</sup>. Additionally, Shi *et al* found that cardiac injury was associated with a higher risk of in-hospital mortality<sup>[18]</sup>. Furthermore, a report of the National Health Commission of China showed that 11.8% of COVID-19 patients without obvious CVD had raised levels of troponin or cardiac arrest during hospitalization. In Seattle, Bhatraju *et al* demonstrated that troponin concentrations were elevated in several patients early in their ICU stay<sup>[19]</sup>. Besides myocardial injury, pathological analysis also revealed that microvascular inflammation and microvascular thrombi occurred in the lung and other injured organs of patients with COVID-19. For patients with pre-existing CVD, SARS-CoV-2 infection increased their propensity to acquire the infection, and they had worse COVID-19 outcomes<sup>[20]</sup>. Although cardiovascular damage is common in patients with COVID-19, the exact mechanisms of cardiovascular system involvement in COVID-19 remain unclear. Potential mechanisms include ACE2-dependent myocardial damage, hypoxia-induced excessive intracellular calcium, and cytokine storm<sup>[21, 22]</sup>. Considering that these mechanisms are closely related to cytokine cascades and inflammatory signaling pathways, the systemic inflammatory response and immune system disorders during disease progression may play a pivotal role.

## 2 IMPACTS OF COVID-19 ON MENTAL HEALTH

With the outbreak of COVID-19, increasing concerns and information are affecting the mental health of people globally<sup>[13, 23]</sup>. A web-based cross-sectional survey from China showed that younger people (<35 years old), people spending too much time focusing on the pandemic, and medical staff had a more severe mental burden, such as generalized anxiety disorder and poor sleep quality<sup>[24]</sup>. In Italy, an early report on the general population found that about 38% of the individuals manifested mild or moderate-to-severe psychological distress related to the COVID-19 outbreak<sup>[25]</sup>. Facing the most extreme of circumstances, medical workers are on the front line of health and social care. Besides inadequate protection against contamination, they also need to overcome overwork, insomnia, frustration, and isolation<sup>[26]</sup>. An online survey completed by antiepidemic nurses from China revealed that nurses fighting against COVID-19 were generally under pressure and anxiety related to working hours

per week<sup>[27]</sup>. Maben *et al* thought that to “get through”, the COVID-19 pandemic, some resilience is needed, but nurses need the whole public to support them with specific actions and resources<sup>[28]</sup>.

## 3 NEUROIMMUNE MECHANISM OF COVID-19-RELATED DAMAGE OF THE CARDIOVASCULAR SYSTEM

### 3.1 Neuroimmune Interaction

The nervous system and the immune system have evolved to modulate homeostasis and to respond to threats. The nervous system provides a nearly instantaneous protection through releasing neurotransmitters, and the immune system responds to infection and injury via inflammation. The interaction between the immune system and the nervous system is multidimensional and multifactorial. In the brain, the dialogue between neurons and myeloid cells plays a key role in the pathophysiological processes of autoimmune diseases, infections, and injuries<sup>[29]</sup>. In the gut, the crosstalk of the enteric nervous system and immune cells can respond to a variety of dietary products, diverse microbiota, and metabolites<sup>[30]</sup>. On the one hand, activated diverse immune cells by the pathogen-related molecular model and the damage-related molecular model can upregulate cytokines like interleukin (IL)-6, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which influences receptors or afferent neurons at the site of infection or injury<sup>[31]</sup>. On the other hand, efferent neurons can regulate levels of TNF- $\alpha$  and other inflammatory molecules via acetylcholine binding and cholinergic receptors<sup>[32]</sup>. Considering that the COVID-19 pandemic has caused severe mental health problems, neuroimmune interactions might play a key role in COVID-19-related cardiovascular damage.

### 3.2 Cytokine Storm in Cardiac Injury of COVID-19 Patients

A cytokine storm, or exaggerated systemic inflammation, is a hallmark of severe disease. Early reports of fulminant myocarditis have suggested that myocardial inflammation might play a pivotal role in cardiac injury during the process of viral infection<sup>[33, 34]</sup>. Likewise, many studies have suggested that patients with severe COVID-19, similar to severe acute respiratory syndrome and Middle East respiratory syndrome-related coronavirus patients, may have cytokine storm syndrome, suggesting that mortality may be due to virus-induced hyperinflammation<sup>[35]</sup>. Furthermore, Zheng *et al* considered that the proposed mechanism of myocardial injury in COVID-19 patients involved cytokine storms triggered via an imbalanced response of type 1 and 2 T helper cells<sup>[21]</sup>. In COVID-19 patients, clinical data have revealed that the cytokine storm is characterized by an elevation of many inflammatory

markers, including IL-6, IL-2, IL-7, TNF- $\alpha$ , monocyte chemoattractant protein-1, macrophage inflammatory protein-1 alpha, interferon gamma-induced protein 10, C-reactive protein, granulocyte colony-stimulating factor, procalcitonin, and ferritin<sup>[8, 17, 36]</sup>. These biomarkers are not just indicators of infection-related inflammation but are also associated with severe cardiac injury and high mortality.

The immune response can influence the function of the central nervous system, contributing to neurodegenerative processes, psychological stress, and cognitive decline<sup>[37, 38]</sup>. In turn, evidence indicates that mental problems contribute to the levels of inflammatory cytokines. In research of emotion regulation and immune function, bereaved spouses who used expressive suppression as a strategy of emotion regulation tended to have higher levels of proinflammatory cytokines, such as IL-17A, IL-2, IL-6, TNF- $\alpha$ , and interferon-gamma<sup>[39]</sup>. The neuroimmune theory of depression also describes a causal relationship between depression and proinflammatory cytokines<sup>[40]</sup>. Findings in animals and in major depressive disorder patients have revealed that a large number of inflammatory cytokines are activated, thus contributing to behavioral symptoms like depression<sup>[41–44]</sup>. It seems that the alteration of pro- and anti-inflammatory cytokine levels can be used as a potential biomarker for the mental health burden.

### 3.3 Hypothalamus-Pituitary-Adrenal Axis Pathway

The social-signal-transduction theory suggests that humans who experience adversity or threats have increased levels of proinflammatory cytokines, which in turn can lead to personal behavioral changes, such as a sad mood, anhedonia, fatigue, or social-behavioral withdrawal<sup>[45]</sup>. Studies have shown that psychological stress or sleep deprivation can cause profound pathophysiological effects on the neuroimmune and endocrine regulatory systems, thereby contributing to modulating stress hormones and proinflammatory markers<sup>[14, 46–48]</sup>. Specifically, the HPA axis can regulate the balance of inflammatory responses by modulating the expression of glucocorticoids (e.g., cortisol). In other words, activation of the hypothalamus-pituitary-adrenal (HPA) axis results in higher levels of glucocorticoids, thus causing inflammatory suppression, downregulation of proinflammatory cytokine levels, and promotion of anti-inflammatory cytokine expression<sup>[49]</sup>. In some inflammation-related diseases such as hepatic cholestasis, depression, and chronic fatigue syndrome, the HPA axis fails to activate and maintain immune balance owing to feedback-regulatory insufficiency and the desensitization of glucocorticoid receptors<sup>[50]</sup>. Therefore, facing the challenge of COVID-19, the mental health burden of infected patients may cause overdrive of the HPA axis, downregulation of the glucocorticoid receptor, and an increase of proinflammatory cytokines, thus

contributing to cardiac injury.

### 3.4 Roles of the Autonomic Nervous System

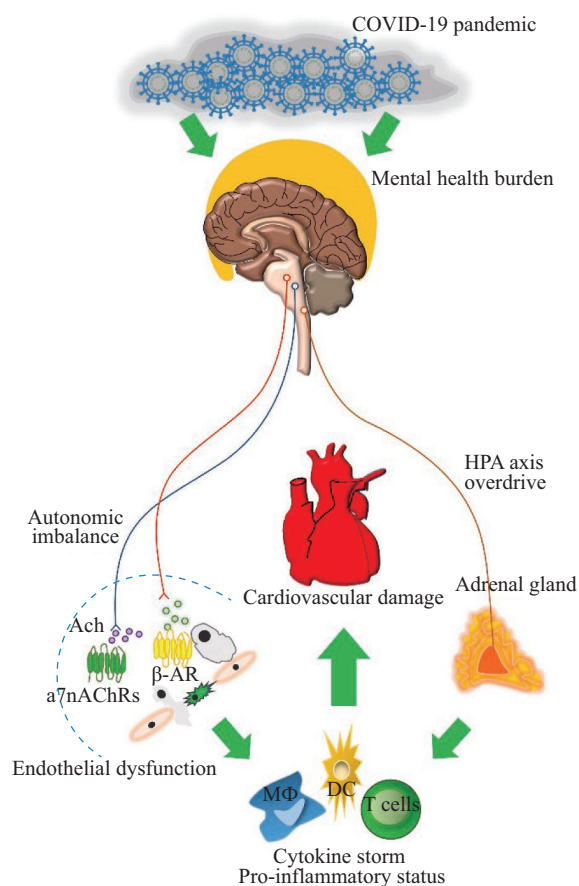
The autonomic nervous system (ANS) consists of the sympathetic nervous system with the major neurotransmitter norepinephrine/epinephrine and the parasympathetic nervous system with the primary neurotransmitter acetylcholine. With the expression of  $\beta_2$  adrenergic receptors, the sympathetic nervous system can induce multiple anti-inflammatory responses via the lymph glands and the spleen. For example, Ortega *et al* have revealed that  $\beta_2$  adrenergic receptors modulate macrophage-mediated inflammatory responses<sup>[51]</sup>. In addition, Ağaç *et al* have found an important role of the sympathetic nervous system in inhibiting inflammation through driving rapid IL-10 secretion<sup>[52]</sup>. In fact, efferent vagal nerves influence immune responses via acetylcholine coordinating with acetylcholine receptors, suppressing macrophage activation, and releasing cytokines such as TNF- $\alpha$ ; this is called the cholinergic anti-inflammatory pathway<sup>[53]</sup>. Both the sympathetic nervous system and the parasympathetic nervous system are highly coordinated in a dynamically balanced manner with the ever-changing microenvironment. In turn, breaking ANS homeostasis, which is characterized by sympathetic neuron overactivity or vagal neuron underactivity, is a pivotal contributor to adverse cardiac outcomes related to mental problems<sup>[54]</sup>. Kadoya and Koyama have reported the complex relationships of ANS dysfunction, atherosclerosis, and inflammation<sup>[15]</sup>. In a murine model of angiotensin II-mediated hypertension, Dorey *et al* have reported that an altered heart rate variability was associated with impaired ANS signaling<sup>[55]</sup>. Therefore, the altered sympathovagal balance may play a significant role in the complex pathophysiological cascade connecting the mental health burden with COVID-19-related cardiovascular damage in COVID-19 patients.

### 3.5 Roles of Endothelial Dysfunction

Microvascular inflammation and microvascular thrombosis are key pathological features in COVID-19, and the mechanism may be related to endothelial dysfunction, which makes the vessel wall vulnerable to leukocyte adherence, inflammatory cell infiltration, prooxidation, platelet activation, and impaired coagulation. Okada *et al* also considered that vascular endothelial injury can exacerbate COVID-19<sup>[56]</sup>. The endothelial dysfunction increases the levels of proinflammatory cytokines, which activate inflammatory pathways and contribute to thrombus formation and vascular occlusion, resulting in myocardial infarctions and strokes<sup>[57–60]</sup>. Additionally, increasing evidence has demonstrated that the mood state might have effects on the endothelial function<sup>[61, 62]</sup>. In a mouse carotid artery model, the stressed mice had increased levels of endothelial-function markers,

such as vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1), and accelerated damage of arterial endothelial cells<sup>[63]</sup>. Likewise, repeated social defeat promotes the expression of VCAM-1 and ICAM-1 in the vasculature of brain regions referring to fear and anxiety responses<sup>[64]</sup>. Furthermore, in a clinical study, Jess *et al* have found that chronicity of mental symptoms contributed to vasculopathy in a dose-dependent fashion and that poorer endothelial function occurred in patients with more manic/hypomanic symptoms<sup>[65]</sup>. Taken together, the mental health burden might be a vital accomplice for COVID-19-related vascular inflammation and thrombosis via inducing endothelial dysfunction.

A summary of the possible neuroimmune mechanisms connecting cardiovascular damage and COVID-19 is given in fig. 1.



**Fig. 1** Summary of the possible neuroimmune mechanisms connecting cardiovascular damage and COVID-19  
HPA: hypothalamus pituitary adrenal; β-AR: β adrenergic receptor; Ach: acetylcholine; α7nAChR: α7 nicotinic acetylcholine receptor; DC: dendritic cells; Mφ: macrophages

#### 4 CONCLUSION

The principal challenge of COVID-19 for humans now exacerbates their mental health burden. Additionally, increasing evidence has shown that

COVID-19-related cardiovascular damage increases the mortality and the poor prognosis of infected patients<sup>[20, 66, 67]</sup>. In this review, complex pathophysiological mechanisms connecting neuroimmune interactions and cardiovascular disease revealed that the mental health burden might be a pivotal accomplice causing COVID-19-associated cardiovascular damage. Specifically, the proinflammatory status of patients with a terrible mood state is closely related to overdrive of the HPA axis, sympathovagal imbalance, and endothelial dysfunction, which lead to an increased risk of developing cardiovascular injury during COVID-19. Therefore, during the prevention and treatment of cardiovascular complications in COVID-19 patients, particular attention should be given to relieve the mental health burden of these patients.

#### Conflict of Interest Statement

On behalf of all authors, the corresponding authors state that there are no conflicts of interest.

Author Nian-guo DONG is a member of the Editorial Board for Current Medical Science. The paper was handled by other editors and has undergone rigorous peer review process. Author Nian-guo DONG was not involved in the journal's review of, or decision related to, this manuscript.

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