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Adverse effects of sympathetic activation should not be neglected during the coronavirus disease 2019 pandemic

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The ongoing coronavirus disease 2019 (COVID-19) pandemic has resulted in considerable morbidity and mortality worldwide. Furthermore, the number of infected individuals is rising rapidly. This disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belonging to the β-coronavirus cluster; this cluster also comprises the viruses causing severe acute respiratory distress syndrome (SARS) and Middle East respiratory syndrome. Similar to SARS-coronavirus (CoV), SARS-CoV-2 exploits angiotensin-converting enzyme 2 (ACE2) to invade its target cells; however, SARS-CoV-2 has a higher binding affinity for ACE2. Therefore, unlike SARS-CoV, which can be efficiently contained, SARS-CoV-2 is more infectious and difficult to control.

SARS-CoV-2 mainly affects the respiratory tract where ACE2 is highly expressed and causes a mild flu-like syndrome in the majority of the cases. However, some patients with severe disease can rapidly progress to pneumonia, acute respiratory distress syndrome (ARDS), and shock. Although its prevalent manifestation and cause of death is ARDS, increasing evidence indicates that patients with cardiovascular risk factors and pre-existing cardiovascular diseases, such as hypertension, diabetes mellitus, and ischemic heart disease, seem to have a higher risk of morbidity and mortality.[1] Furthermore, increasing clinical and epidemiological evidence suggests that besides pneumonia, major cardiovascular complications including cardiac injury, arrhythmias, and blood pressure disorders, can occur in a considerable number of patients with COVID-19. These complications have been observed even in patients without underlying cardiovascular disease and are associated with worse prognosis. ACE2 is widely expressed in not only the lungs but also the cardiovascular system. Therefore, cardiovascular complications are thought to be attributed to a direct viral infection or an indirect injury owing to a systemic inflammatory response, called cytokine storm. However, pathological studies have reported scarce interstitial mononuclear inflammatory infiltrates in the heart tissue and lack of substantial myocardial damage in patients with COVID-19, suggesting that COVID-19 might not directly impair the heart.[2] In a recently reported case of a 64-year-old SARS-CoV-2-positive woman, neither myocarditis nor cytokine storm was reported as probable mediators of the recurrence of depressed cardiac function, given the relatively low biomarker levels.[3] In this case, the patient developed profound cardiac decompensation during the SARS-CoV-2 infection, characterized by a reduced left ventricular ejection fraction accompanied by cardiogenic shock and proclivity for tachyarrhythmias, which suggested that the sympathetic nerves were being over-activated. A recent study also reported a modestly lower likelihood of a positive result for COVID-19 among patients using beta-blockers which can prevent sympathetic activation.[4] Therefore, before the mechanisms of cardiovascular complications accompanying SARS-CoV-2 infection are well established, the damage induced by sympathetic over-activation needs adequate awareness. The sympathetic nervous system plays a prominent role in cardiovascular disease. In the early stages of cardiovascular disease, it often manifests as a compensatory activation of the sympathetic nerves, closely associated with disease severity. Additionally, persistent activation of the sympathetic nervous system accelerates disease progression. The persistent activation of the sympathetic nervous system greatly contributes to the pathogenesis of chronic heart failure, ventricular arrhythmias, and essential hypertension, all of which are common

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cardiovascular complications in patients with COVID-19. The activation of the sympathetic nervous system also triggers Takotsubo syndrome inducing transient heart dysfunction, which is often ignored and misdiagnosed. In the early stages of acute myocarditis, reverse Takotsubo syndrome is observed in patients with COVID-19, which may be induced by the activation of the sympathetic nervous system.[5] Similar to COVID-19, tachycardia is a common cardiovascular manifestation of SARS, and persists till the third week of hospitalization. Such long-lasting tachycardia can possibly occur because of sympathetic over-activation.[6] Moreover, pre-existing cardiovascular diseases, including hypertension, diabetes mellitus, and ischemic heart disease, are characterized by pronounced sympathetic activation, which may be closely and directly associated with COVID-19 severity.

Various mechanisms of sympathetic activation following SARS-CoV-2 infection could include but are not limited to the following aspects: (1) the carotid body chemosensory input to the brainstem contributes to over-activation of the sympathetic nervous system due to hypoxia induced by the respiratory distress syndrome; (2) the neuroinvasive potential of SARS-CoV-2 may induce neuroinflammation in significant central sympathetic sites, such as the nucleus of the solitary tract (NTS), hypothalamic paraventricular nucleus (PVN), and rostral ventrolateral medulla (RVLM); (3) inflammatory cytokines released during the systemic inflammatory response after virus invasion may penetrate the blood-brain barrier and impair the NTS, PVN, and RVLM; and (4) extreme anxiety leads to further endogenous catecholamine release. Consequently, it is worth considering whether inhibitors of the sympathetic nervous system, such as central sympatholytic drugs, imidazoline receptor agonists, and beta-blockers might achieve better results in the absence of a specific treatment or vaccine for COVID-19.

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Conflicts of interest

None.

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