

COMMENTARY

Day-to-day blood pressure variability in COVID-19: A biomarker of disrupted central autonomic network

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In this issue of the *Journal*, the paper by He and coworkers¹ provides several new insights into the significant relationships of day-to-day systolic blood pressure (SBP) variability, that is, standard deviation (SD), coefficient of variation (CV), and variability independent of mean (VIM)—with acute respiratory distress syndrome (ARDS) and mortality in 702 COVID-19 patients with hypertension. In addition, increased blood pressure (BP) variability was associated with severe inflammation and myocardial injury.¹

In COVID-19, systemic inflammation,² endothelial dysfunction,³ breakdown of blood-brain-barrier (BBB),⁴ and endocardial endothelial barrier, respectively, and alterations in cardiac response⁵ have been considered to play pivotal roles in the pathophysiology of BP dysregulation leading to increased BP variability that could precede ARDS and critically ill in COVID-19 patients with hypertension.¹

In COVID-19, an excessive inflammation phase, so called a “cytokine storm”, leads to end tissue damage and organ failure.⁶ A fatal cytokine storm involves the release of considerable amounts of proinflammatory cytokines including IL-6 and TNF- α .⁶ Under the influence of these proinflammatory cytokines, BBB integrity is locally impaired, enabling the influx of potentially neurotoxic endo- and xenobiotics into the brain parenchyma. This ultimately, via dysregulation of the central autonomic network (CAN) comprising the insular cortex (Ic), cingulate cortex, amygdala, hypothalamus, periaqueductal gray, parabrachial nucleus, nucleus of the tractus solitarius, and rostral ventrolateral medulla can lead to pathological activation of the sympathetic nervous system (SNS) predominance (Figure 1).^{2,7,8}

The carotid bodies, the principal peripheral chemoreceptors, are suggested to be a site of SARS-CoV-2 invasion because they are the site of the local expression of the receptor of angiotensin-converting enzyme.⁹ On the other hand, COVID-19 enters through nasal infection

and reaches the central nervous system through the olfactory bulb, causing neuroinflammation and demyelination of neuronal cells. In a recent systematic review, a predominant abnormality of the Ic was reported in patients with COVID-19.¹⁰ Increased peripheral arterial chemosensitivity and reflex SNS overactivation due to Ic dysregulation might be associated with increased day-to-day BP variability in COVID-19 patients with hypertension reported by He and coworkers.¹

In the spontaneously hypertensive rat, an increased SNS activity was shown to be attributed to the alterations of neurovascular unit in the Ic leading to changes in the neurogenic BP elevation.¹¹ On the other hand, Ic was reported to store immune-related information using activity-dependent cell labeling in mice.¹² Clinical studies revealed that the damage involved the Ic has associations with increased BP variability, myocardial injury, a higher plasma level of catecholamine, ARDS, and a poor prognosis.^{13–15}

In the Jichi Medical School ABPM Study Wave 2 Core, the left Ic atrophy had a significant correlation with the level of brain natriuretic peptide, the right Ic atrophy had a significant correlation with the level of noradrenaline.^{14,16} In addition, the left posterior Ic damage in acute ischemic stroke was associated with increased BP variability.¹⁷ Patients with the left Ic-involved stroke had a significant decrease in baroreflex sensitivity.¹⁸ Ic-involved stroke was also associated with increased cardiac troponin T.^{19,20} Thus, in COVID-19, imbalance in autonomic nervous system and dysregulation in immune system might be caused simultaneously by disruption of CAN including Ic due to BBB breakdown.

Under physiological circumstances, the endothelial barrier selectively regulates endothelial permeability and fosters vascular integrity in the different sections of the vascular tree.^{3,21} Regardless of the mechanism of endothelial injury, breaches in the physical integrity of

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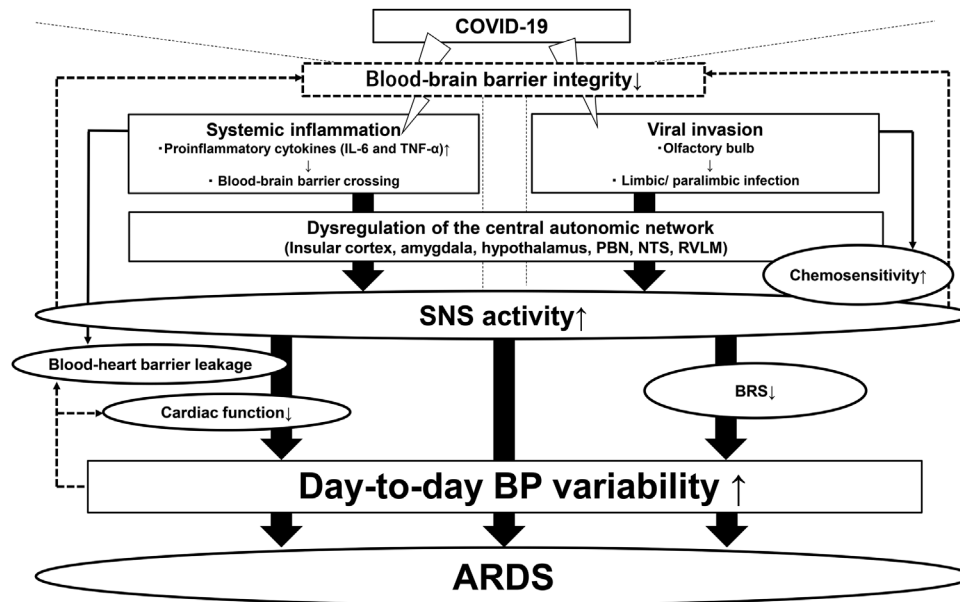


FIGURE 1 A scheme for the relationship between COVID-19 infection and increased day-to-day BP variability moderated by blood-brain barrier integrity. COVID-19 indicates coronavirus disease 2019; PBN, parabrachial nucleus; NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla; SNS, sympathetic nervous system; BRS, baroreceptor sensitivity; BP, blood pressure; ARDS, acute respiratory distress syndrome

the endothelial barrier leads to capillary leak in the microvasculature, overturning the usually semi-permeable properties of the endothelium and contributing to inappropriate leakage of vascular contents into the tissue compartment and extracellular space.^{22,23} The endothelium, whether it is in the endocardium or in a coronary or capillary, is the primary barrier against blood-heart barrier (BHB) dysfunction.^{5,24} Increased BP variability has been associated with lower flow-mediated dilation.²⁵ In COVID-19, higher BP variability might augment endothelial dysfunction as well as BHB leakage leading to cardiac overload and cardiac injury (Figure 1).

Using an in-vitro model of BBB consisted of immortalized murine microvascular endothelial cell line,²⁶ the molecular effects of exposure to catecholamines (dopamine, norepinephrine, epinephrine) and cytokines of pro-inflammation (IL-6 and TNF- α) were analyzed. BBB integrity was clearly affected by catecholamine and pro-inflammation under the conditions of oxygen glucose deprivation. Most proteins of the established BBB model were downregulated. Those structures could be interpreted as the basis of the molecular pathophysiology of the cerebral vasculature and elucidation of the involved targets of these cytokines and their mechanisms of action might comprise a potential therapeutic target for BBB under condition of increased SNS activity concomitant with hypoxia in COVID-19.²⁷

In patients hospitalized with COVID-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization.²⁸ Glucocorticoids modulate inflammation-mediated lung injury, potentially pathologic pulmonary epithelial mesenchymal conversion, and thereby reduce death. While the BBB integrity could be compromised in COVID-19, therapeutical strategies for neuroin-

flammation in COVID-19 include treatment with glucocorticoids. At the molecular level, hydrocortisone induces an increase of occludin in protein and mRNA levels by activation of the glucocorticoid receptor.²⁹ Thus, the earlier use of glucocorticoids in COVID-19 might be associated with BBB protection, and could reduce day-to-day SBP variability via CAN preservation. Moreover, at the pulmonary epithelial cell level, administration of glucocorticoids might help prevent the pulmonary epithelial mesenchymal conversion,³⁰ as it is characteristic for COVID-19 lungs. The underlying molecular mechanisms are currently under investigation in our laboratory.

Until now, there have been few reports assessing the relationship between day-to-day BP variability and mortality in COVID-19. In addition to strict BP control, it might be important to minimize day-to-day BP variability in order to reduce the mortality in COVID-19 patients. The data presented in the study by He and coworkers¹ thus make an important contribution, provided that they are considered within the context of the precise pathophysiology underlying the relationship between COVID-19 infection and day-to-day BP variability.

CONFLICT OF INTEREST

The authors have no competing interests.

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