Maladaptive Alterations of Autonomic Nerve System in Cardiovascular Disorders

Yukiteru Nakayama, MD and Katsuhito Fujiu, MD

(Excerpt:)

Sudden unexpected nocturnal death syndrome (SUNDS) occurs predominantly in Southeast Asia, and the young healthy victims are struck by unexplained deaths during nocturnal sleep. The predilection time implies that the balance of the autonomic nervous system is associated with arrhythmogenesis. Mongkonsiri, et al. reported that healthy subjects with a family history of SUNDS showed blunted responsiveness to cold pressor testing and steady exercise during the nighttime, indicative of decreased sympathetic and increased parasympathetic nerve activity. Regarding the autonomic imbalance in patients with Brugada syndrome, a disease relevant to SUNDS, inconsistent results have been reported. Some papers have revealed that adrenergic dysfunction was observed in diseased groups, while others reported no differences in heart rate variability. However, Brugada syndrome and SUNDS are regarded as different diseases in that the latter is more likely a multifactorial disorder caused by both intrinsic pathogenic genes and external environmental factors. Various factors implicated with susceptibility to SUNDS, including diet, lifestyle, and work intensity could contribute to the tuning of the autonomic nervous system rather than the direct effects of genetics, as previously reported.

From the Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan and Department of Advanced Cardiology, The University of Tokyo, Tokyo, Japan.

Address for correspondence: Yukiteru Nakayama, MD or Katsuhito Fujiu, MD, Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan. E-mail: ynakayama-tky@umin.ac.jp or fujii-tky@umin.ac.jp

Received for publication November 30, 2018. Revised and accepted December 5, 2018.

doi: 10.1536/ihj.18-677

All rights reserved by the International Heart Journal Association.
failure models via c-fos, p38, and ERK1/2 pathways, and augmented aldosterone was also shown to contribute to increased AT1R levels.\textsuperscript{13} Upregulated AT1 signaling activates both the transcription factor activator protein-1 (AP-1) and NAD(P)H oxidase.\textsuperscript{14} AP-1 regulates inflammatory cytokines and NAD(P)H oxidase is implicated in the generation of reactive oxygen species (ROS). This modulation of the brainstem in heart failure is supported by the evidence that AT1R antagonists blocked the cascades. In the PVN as well, heart failure leads to AT1R expression at higher levels and upregulated RAS signaling, which induces inflammatory cytokines, activates NAD(P)H oxidase to increase oxidative stress,\textsuperscript{15} and impairs neuronal nitric oxide synthase (nNOS). NO production in the PVN has sympahto-inhibitory effects coupled with an increased expression of GABA and inhibitory action of glutamate,\textsuperscript{16} while ROS enhances excitatory inputs through increasing glutamatergic and decreasing GABAergic transmission. Although accumulating evidence indicates a key role for inflammation in the sympathoexcitatory response, the direct underlying mechanism of the linkage has yet to be fully elucidated. Localized inflammatory cytokine expression activates microglia in the PVN,\textsuperscript{17} brain perivascular macrophages,\textsuperscript{18} and astrocytes in RVLM.\textsuperscript{19} These histo-

**Figure.** Neural circuits involved in autonomic nervous system in heart failure. Baroreceptor nerve inputs transmit to the vasomotor center in the brainstem, where the tonus of sympathetic nerves is set down after integration with information from the forebrain.
logical remodelings could contribute to a shift of the set point. Structural alterations also occur in downward neural circuits. Inflammatory cytokines were induced in stellate ganglia and dorsal root ganglia after the acute phase of myocardial infarction, and highly elevated apoptotic activity and at the same time nerve sprouting and hyperinnervation were observed after chronic myocardial infarction.20,21)

Numerous studies have explored the pivotal roles of brain RAS, NO, and inflammatory cytokines in the abnormal regulation of autonomic nerve activity in heart failure. Over a decade, new technologies including optogenetics and single cell transcriptomes have enabled further findings in the field of neuroscience. It has been only recently clarified that the mechanically activated ion channels PIEZO1 and PIEZO2 are together identified as aortic baroreceptors.22) The relationship between cardiovascular diseases and autonomic imbalance should be examined in greater detail in the future.

Disclosures

Conflicts of interest: None.

References