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EDITORIAL COMMENT

The Autonomic Nervous System and Cardiovascular Health and Disease

A Complex Balancing Act*

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The cardiac autonomic nervous system (ANS) is a crucial component in physiological and pathological responses of the cardiovascular system. Through its 2 branches, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) nervous systems, as well as effector molecules including norepinephrine (NE) and acetylcholine, the ANS orchestrates many events that allow for appropriate blood pressure (BP), heart rate (HR), and vasoregulatory responses to routine daily stimuli. Dysregulation of this system due to aging, acute and chronic stress, organic and idiopathic and other causes contributes to cardiovascular pathology, including hypertension, ischemic heart disease, arrhythmias, and congestive heart failure, and often contributes to fatal outcomes.

Heart failure with reduced ejection fraction (HFrEF) is characterized by neurohumoral activation mediated by the SNS and renin-angiotensin system (1). Sympathetic hyperactivity is evident by increased central sympathetic outflow and plasma NE levels, with NE spillover of up to 50-fold compared to that in controls (2,3). Even in HF patients with preserved EF (HFpEF), sympathetic hyperactivity represented by increased skeletal muscle nerve activity may contribute to the development of diastolic dysfunction (4). ^{123}I-labeled *meta*iodobenzylguanidine (MIBG) cardiac nuclear imaging assesses cardiac adrenergic nerve function and provides prognostic information for risk stratifying patients with HF (5).

Sympathetic hyperactivity in HF is related to a combination of suppression of the cardio-inhibitory reflexes, such as the baroreflex, and augmentation of the sympatho-excitatory reflexes, such as the afferent sympathetic reflex or the arterial chemoreceptor reflex (6). Within the central nervous system, both angiotensin II and aldosterone have been implicated in sympathetic activation through increased catecholamine release and decreased synaptic reuptake (7,8). This sympathetic hyperactivity affects excitation-contraction coupling and calcium signaling, thereby enhancing apoptosis and leading to progression of HF (9,10).

Other clinical conditions further implicate ANS balance playing a role in ventricular dysfunction. Stress cardiomyopathy, also known as Takotsubo cardiomyopathy or broken heart syndrome, although

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likely under-reported, appears to have the highest prevalence in post-menopausal women presenting with suspected acute coronary syndrome (11,12). Stress cardiomyopathy is characterized by an abnormal response to a catecholamine surge due to an emotional or a physical stressor, which leads to symptoms of chest pain and dyspnea, electrocardiographic changes, troponin elevation, and acute HF. In the most common variant of stress cardiomyopathy, apical ballooning with akinesis occurs with basal hyperkinesis, although other forms have been described (13). Apical ballooning is thought to be related to regional variation in the density of β-adrenergic receptors and increased sympathetic activity at the area of akinesis (14). A possible mechanism for high post-menopausal female prevalence may include the age-specific decrease in vagal tone and baroreceptor sensitivity from reduced estrogen levels, thereby augmenting the catecholamine-mediated stress response. Increased sympathetic activity and impaired baroreflex sensitivity has been shown in this stress cardiomyopathy (15). It remains unclear why most cases present in women, but recently, coronary endothelial and microvascular dysfunction have been implicated (16–18).

The prospective study of a 100 Dutch patients with HFrEF (left ventricular ejection fraction of <40%) who underwent mental stress testing adds to this understanding of the role the ANS balance plays in ventricular dysfunction. Kupper et al. (19) report that a reduced cardiovascular (diastolic BP) reactivity was associated with increased mortality on follow-up. The study further shows that increased mortality in chronic HF is associated with increased resting HR, reflecting resting sympathetic overdrive, suggesting that the increased mortality with lower blood pressure reactivity to mental stress is due to an exhausted sympathetic/cardiovascular response. These findings elaborate on the mechanism of benefit noted in prior reports and clinical trials of beta blockade in heart patients (20).

In this issue of *JACC: Heart Failure*, Kupper et al. (19) further demonstrate the complex balancing act that ANS regulation plays in cardiovascular health and disease. Notably, a negative HR response (a drop in HR in response to mental stress) was associated with better survival, whereas a blunted diastolic BP response was associated with worsened survival (19). Although the authors discuss the fact that different mechanisms may underlie the blunted BP response compared to the reduction in HR (e.g., HR is relatively more regulated by autonomic control, whereas BP is more closely associated with endothelial dysfunction), previous mental stress testing work demonstrates a predictable, direct relationship between the R-R interval and BP response, such that a higher BP response is associated with slowing of the HR (21). The current study results suggest that this anticipated response, consistent with an intact cardiac ANS, in the setting of HF may be protective.

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Taken together with previous reports, these new data are novel and hypothesis generating. We have proposed previously that PNS/SNS imbalance of the cardiac ANS is a potential mechanistic and therefore therapeutic target for ischemia (22), arrhythmias (23), and the metabolic syndrome (24), using mind-body and alternative and complementary interventions. Ongoing research in both HFrEF and HFpEF should further test ANS balance as a mechanistic pathway and therapeutic target, using both pharmacologic and mind-body techniques (25).

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