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STATE-OF-THE-ART REVIEW

Neuromodulation of the Failing Heart

Lost in Translation?

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SUMMARY

Sympathovagal imbalance contributes to progressive worsening of heart failure (HF) and is associated with untoward clinical outcomes. Based on compelling pre-clinical studies that supported the role of autonomic modulation in HF models, a series of clinical studies were initiated using spinal cord stimulation, vagus nerve stimulation, and baroreceptor activation therapy in patients with HF with a reduced ejection fraction. Whereas the phase II studies with baroreceptor activation therapy remain encouraging, the larger clinical studies with spinal cord stimulation and vagus nerve stimulation have yielded disappointing results. Here we will focus on the pre-clinical studies that supported the role of neuromodulation in the failing heart, as well provide a critical review of the recent clinical trials that have sought to modulate autonomic tone in HF patients. This review will conclude with an analysis of some of the difficulties in translating device-based modulation of the autonomic nervous system from pre-clinical models into successful clinical trials, as well as provide suggestions for how to move the field of neuromodulation forward.
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OVERVIEW OF THE CARDIAC AUTONOMIC NERVOUS SYSTEM

Details of the complex regulation of the autonomic nervous system (ANS) have been provided in several recent reviews and will be discussed here only briefly in order to provide the proper context for the discussion of the clinical studies of device-based modulation of ANS ("neuromodulation") in heart failure (HF) (1,2). ANS consists of the parasympathetic nervous system and the sympathetic nervous system (SNS). Physiologically, these 2 systems are diametrically opposed, yet work together synergistically in a reciprocal manner, in order to provide the cardiovascular system with the ability to respond quickly to both internal and external stimuli (3). Both the SNS and the ANS are reflex circuits composed of "motor" (efferent) fibers that convey information from the central nervous system to the heart (Figure 1) and "sensory" (afferent) sympathetic and parasympathetic fibers that convey information from the heart to the central nervous system. The heart also receives afferent parasympathetic input from a series of mechanosensitive nerve endings in large arteries and the carotid sinuses, collectively referred to as baroreceptors, because they are sensitive to changes in blood pressure and blood volume. The baroreceptors from the carotid arteries have axons in the glossopharyngeal nerve, and those from the aorta have axons that travel in the vagus nerve. The baroreflex is a major homeostatic mechanism for maintaining blood pressure and is responsible for controlling the afterload of the heart. Baroreceptors are activated by the opening of mechanosensitive ion channels within the sensory terminals, which in turn activate afferent fibers that terminate in the nucleus tractus solitarius in the medulla oblongata. Increased baroreflex activity (e.g., in hypertension) results in a

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ABBREVIATIONS AND ACRONYMS

ANS = autonomic nervous system

BAT = baroreceptor activation therapy

HF = heart failure

HFrEF = heart failure with a reduced ejection fraction

LV = left ventricular

LVEF = left ventricular ejection fraction

MSNA = muscle sympathetic nervous activity

MI = myocardial infarction

NE = norepinephrine

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

OMT = optimal medical therapy

SCS = spinal cord stimulation

SNS = sympathetic nervous system

VF = ventricular fibrillation

VNS = vagus nerve stimulation

VT = ventricular tachycardia

reflex increase in parasympathetic activity that triggers a reflex inhibition of sympathetic tone, thus restoring autonomic balance. Conversely, decreased baroreflex activity (e.g., in hypotension) results in withdrawal of parasympathetic tone that results in a reflex increase in sympathetic tone.

SYMPATHOVAGAL IMBALANCE IN HEART FAILURE

The clinical syndrome of heart failure with a reduced ejection fraction (HFrEF) is associated with sustained activation of the sympathetic nervous system that is accompanied by a withdrawal of parasympathetic tone (2,4,5). Although these disturbances in autonomic control were initially attributed to loss of the inhibitory input from arterial or cardiopulmonary baroreceptor reflexes, there is increasing evidence that excitatory reflexes may also participate in the autonomic imbalance that occurs in HF (2). Under normal conditions, inhibitory inputs from "high pressure" carotid sinus and aortic arch baroreceptors and the "low pressure" cardiopulmonary mechanoreceptors are the principal inhibitors of sympathetic outflow, whereas discharge from the nonbaroreflex peripheral chemoreceptors and muscle "metaboreceptors" are the major excitatory inputs to sympathetic outflow. The parasympathetic limb of the baroreceptor heart rate reflex is also responsive to arterial baroreceptor afferent inhibitory input. At rest, healthy individuals display low sympathetic discharge and high rate variability. In HF patients, the peripheral baroreflex responses become suppressed ("blunted") as HF worsens (6). Blunting of the peripheral arterial and cardiopulmonary baroreceptors results in a derepression of the sympathetic outflow from the central nervous systems and a net increase in efferent sympathetic nerve activity that is accompanied by decreased efferent parasympathetic tone. Consequently, patients with HF have a loss of heart rate variability and increased peripheral vascular resistance (2).

Dysregulation of the ANS in HF has received considerable attention over the past 3 decades, because of the well-recognized association between increased sympathetic activity and "neurohormonal" activation. Although increased sympathetic stimulation provides short-term support for the cardiovascular system, the sustained activation of the SNS is maladaptive in the long term because it is directly toxic to the heart and circulation and also leads to activation of the renin-angiotensin system, which can also be deleterious to the heart and circulation (reviewed in [7]). However, the role of the parasympathetic nervous system in the pathophysiology of HF is less well understood. In isolated organ preparations, human in vitro data, and in animal models, local muscarinic receptor stimulation results in inhibition of norepinephrine (NE) release from sympathetic nerve terminals (8,9). In vivo, it has been shown that cardiac NE spillover was greater in patients with HF than those with normal LV function, and that infusion with acetylcholine attenuates the amount of NE release in these patients. This effect was not seen in the presence of atropine, suggesting that it is mediated via muscarinic receptor activation (10,11). The ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) trial was the first large multicenter clinical study to examine impairment in vagal activity as a prognostic marker following myocardial infarction (MI). ATRAMI enrolled 1,284 post-MI patients and followed them over a 2-year period and showed that patients with depressed baroreflex sensitivity (a marker of decreased vagal activity) had decreased survival (5). The depressed baroreflex sensitivity was also shown to be associated with a worse New York Heart Association (NYHA) functional class and higher mortality in HF patients. The prognostic value of the depressed baroreflex sensitivity among patients with HFrEF was also observed in the presence of beta-blocker therapy (12,13). These observations have led to the development of various device-based therapies that are designed to restore the sympathovagal imbalance in patients with HF.

THERAPEUTIC MODULATION OF THE AUTONOMIC NERVOUS SYSTEM IN HEART FAILURE

It bears emphasis that many of the current therapies for HFrEF patients reverse the sympathovagal imbalance that develops in HF, including pharmacologic therapy with beta-blockers and angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, exercise training, and cardiac resynchronization therapy (reviewed in [14]). Despite the tremendous progress in treating patients with HF, the great majority of patients with HF will eventually develop worsening HF (15). Thus, there continues to be an unmet need for new therapies for treating patients with HF. To this end, there has been growing interest in directly modulating the ANS as a means of counteracting the sympathovagal