JACC: HEART FAILURE
VOL. 3, NO. 10, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2015.05.008

STATE-OF-THE-ART PAPER

Novel Interventional Therapies to Modulate the Autonomic Tone in Heart Failure

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JACC: HEART FAILURE CME

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CME Objective for This Article: After reading this article, the reader should be able to discuss: 1) the role of the autonomic nervous system (ANS) in the pathophysiology of heart failure; 2) the current state of knowledge related to ANS modulation for the treatment of heart failure; and 3) the implications of these data related to clinical practice and future research.

CME Editor Disclosure: Deputy Managing Editor Mona Fiuzat, PharmD, FACC, has received research support from ResMed, Gilead, Critical Diagnostics, Otsuka, and Roche Diagnostics. Tariq Ahmad, MD, MPH, has received a travel scholarship from Thoratec. Robert Mentz, MD, has received a travel scholarship from Thoratec; research grants from Gilead; research support from ResMed, Otsuka, Bristol-Myers Squibb, AstraZeneca, Novartis, and GlaxoSmithKline; and travel related to investigator meetings from ResMed, Bristol-Myers Squibb, AstraZeneca, Novartis, and GlaxoSmithKline. Adam DeVore, MD, has received research support from the American Heart Association, Novartis Pharmaceuticals, Thoratec, and Amgen.

Author Disclosures: Dr. Singh has received research grants from Boston Scientific, St. Jude Medical, Medtronic, and Sorin Group; and has been a consultant for Boston Scientific, St. Jude Medical, Medtronic, Sorin Group, CardioInsight, and Respicardia. Dr. Chatterjee has reported that he has no relationships relevant to the contents of this paper to disclose.

Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval

Issue date: October 2015
Expiration date: September 30, 2016

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Manuscript received March 18, 2015; revised manuscript received April 17, 2015, accepted May 1, 2015.

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ABSTRACT

Heart failure (HF) represents a significant and expanding public health burden associated with increasing prevalence and exponential growth in related health care costs. Contemporary advances in both pharmacological and nonpharmacological therapies have often been restricted in application and benefit. Given the critical role of the autonomic nervous system (ANS) in maintaining cardiovascular homeostasis in the failing heart, there has been increasing interest in the role of ANS modulation as a therapeutic modality in HF. In this review, we highlight the anatomy of the ANS and its role in the pathophysiology of HF, as well as metrics of its assessment. Given the limitations associated with pharmacological ANS modulation, including lack of specificity and medication intolerance, we focus in this review on contemporary nonpharmacological ANS modulation therapies. For each therapy—vagal nerve stimulation, carotid baroreceptor stimulation, spinal cord stimulation, and renal denervation—we review the rationale for modulation, pre-clinical and clinical assessments, as well as procedural considerations and limitations. We conclude by commenting on novel technologies and strategies for ANS modulation on the horizon. (J Am Coll Cardiol HF 2015;3:786–802) © 2015 by the American College of Cardiology Foundation.

Heart failure (HF) represents a significant and expanding public health burden affecting nearly 25 million patients globally (1,2). In the United States alone, the prevalence of HF is nearly 6 million and is estimated to double by the year 2030 (2). Although contemporary strategies in the management of HF have improved survival after diagnosis, overall mortality remains high because nearly one-half of patients die within 5 years (3). The expanding prevalence of HF, coupled with improved survival after diagnosis, has framed an exponential growth in HF-related costs, estimated to range between $30 and $60 billion, and are expected to more than double in the next 20 years (2,4).

In the face of rising HF morbidity, mortality, and costs, there have been important contemporary advances in both pharmacological (5) and nonpharmacological therapies (6), although their application and benefit are often restricted to a subset of patients (7). In this context, given the long-recognized relationship between autonomic nervous system (ANS) function and HF, there is increasing interest in ANS modulation as a therapeutic modality. In this review, we highlight the anatomy of the ANS and its role in the pathophysiology of HF, as well as metrics of its assessment. We then review contemporary nonpharmacological ANS modulation therapies in HF before commenting on novel technologies and strategies on the horizon.

ANATOMY, REFLEXES, AND REGULATION OF THE ANS

In its most reductive form, the ANS primarily comprises 2 systems: the sympathetic and parasympathetic. The sympathetic nervous system (SNS) serves a predominant cardioacceleratory function, and its activation is associated with augmentation of heart rate (HR), increased ventricular contraction, and enhanced atrioventricular conductivity. In counterbalance, the parasympathetic nervous system (PNS) serves a predominant cardioinhibitory function associated with attenuation of HR and ventricular contraction, reduced arterial stiffness, and increased venous capacitance. The dynamic interaction of these 2 limbs of the ANS, modulated by physiological inputs and reflexes, ultimately regulates the hemodynamic and electrical functions of the heart and vascular system (**Central Illustration**).

Understanding the anatomy of the ANS is critical to defining the scope of its therapeutic targeting and modulation (**Figure 1A**). The SNS output is located in the spinal column (first thoracic to fourth lumbar segments), extending rostrally and caudally to the adjacent paravertebral ganglia forming the sympathetic trunk. SNS signals are carried via pre-ganglionic neurons to post-ganglionic ganglia, which are either located directly on viscera (adrenal cortex, smooth muscle cells of blood vessels) or, in the case of myocardial input, organized into 2 major ganglia (superior cervical and stellate) (9). For myocardial SNS