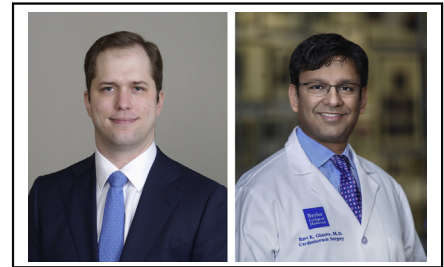


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## Commentary: Stimulating new options for heart failure management

Christopher T. Ryan, MD, and Ravi K. Ghanta, MD



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Treatment for heart failure with reduced ejection fraction (HFrEF) has progressed significantly over the past decade, with significant mortality benefit demonstrated with guideline-directed medical therapy (GDMT) incorporating newer classes of drugs.<sup>1</sup> However, up to 30% of patients with HFrEF are unable to tolerate target doses of GDMT regimens.<sup>1,2</sup> A sizable minority of patients may also be considered “nonresponders,” with progression of HFrEF severity despite optimal GDMT dosing.<sup>3</sup> Ongoing research to identify additional therapeutic options for these patients has focused on components of HFrEF pathophysiology that are incompletely addressed by medical therapy. Neurohormonal dysregulation is a prominent therapeutic target, as autonomic imbalance with excess sympathetic imbalance has been implicated in progression of key components of HFrEF pathophysiology. Proposed mechanisms include persistent myocardial inflammation, arrhythmogenicity, peripheral vasoconstriction, and impaired adaptation to altered ventricular loading conditions.<sup>4</sup>

Surgical techniques for autonomic modulation in heart failure include activation of parasympathetic reflexes through vagal nerve stimulation or baroreceptor activation, or reduction of sympathetic tone through renal denervation or left cardiac sympathetic denervation.<sup>5</sup> Vagal nerve stimulation (VNS), as detailed by Al Rameni and colleagues<sup>6</sup> in

### CENTRAL MESSAGE

An accessible, streamlined operation is described for vagal nerve stimulator implantation, an investigational therapy for neuromodulation in heart failure management.

this issue of *JTCVS Techniques*, is notable for being simpler and less invasive than alternative techniques and permitting therapy titration postoperatively. The surgical technique for VNS implantation primarily incorporates standard surgical techniques and would be anticipated to have a short learning curve, which could greatly facilitate clinical uptake and use. Titrating nerve stimulation would presumably require more intensive training, but this step seems likely to be performed by heart failure cardiologists in clinical practice and outside the surgeon’s purview.

While VNS implantation relies on established pathophysiologic principles, and the approach has been employed successfully in other diseases, it must be emphasized that the procedure remains an investigational therapy for HFrEF. Three clinical trials (Autonomic Regulation Therapy for the Improvement of Left Ventricular Function and Heart Failure Symptoms [ANTHEM-HF], Neural Cardiac Therapy for Heart Failure Study [NECTAR-HF], Increase of Vagal Tone in Heart Failure [INOVATE-HF]) have been completed to date with mixed results and demonstrated efficacy largely limited to surrogate outcomes.<sup>7</sup> The results of the ongoing ANTHEM-HFrEF (Autonomic Regulation Therapy to Enhance Myocardial Function and Reduce Progression of Heart Failure With Reduced Ejection Fraction) pivotal study will advance our understanding of the clinical efficacy of VNS, as this trial has significantly larger planned

From the Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Tex.

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Address for reprints: Ravi K. Ghanta, MD, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, One Baylor Plaza, MC 390, Houston, TX 77030 (E-mail: [Ravi.Ghanta@bcm.edu](mailto:Ravi.Ghanta@bcm.edu)).

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enrollment and more clinically relevant primary outcome measures.<sup>8</sup> Al Rameni and colleagues<sup>6</sup> should be commended for leveraging their own previous experience to demystify the surgical technique for VNS implantation, which could facilitate greater surgeon involvement in clinical trials investigating this unique therapy in the difficult-to-treat refractory HFrEF patient population.

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