JACC: HEART FAILURE
VOL. 4, NO. 2, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2015.11.007

EDITORIAL COMMENT

Spinal Cord Stimulation for Heart Failure in the DEFEAT-HF Study

Lost Battle or Lasting Opportunities?*

Gaurav A. Upadhyay, MD,[a] Jagmeet P. Singh, MD, DPHIL[b]

"I have not failed. I've just found 10,000 ways that won't work."
— Thomas A. Edison (1)

Over the past few decades, pharmacological therapy for heart failure (HF) with reduced ejection fraction has undergone striking advances. Large-scale randomized, controlled trials (RCTs) have established the efficacy of combination therapy with beta-blockers, angiotensin-converting enzyme inhibitors or receptor blockers, aldosterone antagonists, and neprilysin inhibitors. Much of the benefit of these agents is mediated through their impact on the neurohormonal axis and modulation of autonomic tone. Consequently, there has been considerable interest in finding a nonpharmacological approach that is not vulnerable to the inconsistency of patient compliance or the side effects of pharmacotherapy. Spinal cord stimulation (SCS) is one such evolving strategy among a panoply of emerging device-based therapies seeking to exert neurohormonal control, such as vagal nerve, carotid baroreceptor, tragus nerve, and cardiac plexus stimulation. Among these, SCS enjoys the longest history of study in humans.

Centered on the seminal work related to the gate control theory of pain by Melzack and Wall (2,3), electrical stimulation of the dorsal column of the spinal cord was first performed for thoracic pain relief in a patient with metastatic cancer in 1967 (4). Twenty years later, its use was extended to the treatment of refractory angina pectoris (5) and validated across several small RCTs (6). Notably, however, the precise mechanisms of action of SCS have remained elusively multifactorial (7–10). In addition to altering nociception of pain through a direct effect on local neurotransmitters (11,12), there is evidence that SCS induces systemic sympatholysis (13) and reduction in sinus discharge rate mediated through enhanced vagal tone (14). Enthusiasm for SCS has escalated in recent years, largely driven by data from canine models of ischemic heart failure in which SCS significantly reduced ventricular arrhythmic burden (15,16) and also improved left ventricular (LV) contractile function (16). Similar results were also reproduced in porcine ischemia-reperfusion models (17–19), with evidence of significant cardiac sympathetic nerve sprouting and reinnervation, indicative of distinct cellular remodeling with SCS after myocardial infarction (19).

Of note, there has been some previous work in humans exploring the impact of SCS in patients with LV systolic dysfunction. In an early study of adenosine-provoked ischemia, patients demonstrated less deterioration in LV function after adenosine provocation with SCS-on versus SCS-off (20). More recently, the multicenter SCS Heart (Spinal Cord Stimulation for Heart Failure) study reported their results comparing 17 patients actively receiving SCS with 4 nontreated control subjects (21). From a safety endpoint, procedural success was achieved in all patients with no acute complications of the implant. No deaths were reported at 6 months; however, 2 patients experienced ventricular tachyarrhythmia and 2 were hospitalized for HF. Patients receiving SCS

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the [a]Heart Rhythm Center, The University of Chicago Hospital, Chicago, Illinois; and the [b]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Dr. Singh is a consultant for Medtronic, Biotronik, Boston Scientific, St. Jude Medical, LivaNova, and Respicardia; and has received research grants from St. Jude Medical, LivaNova, and Boston Scientific. Dr. Upadhyay has received research grants from Medtronik and Biotronik.

JACC: HEART FAILURE VOL. 4, NO. 2, 2016
FEBRUARY 2016:137–9

demonstrated improved New York Heart Association (NYHA) functional class at 6 months, better self-reported quality of life, improved peak oxygen consumption, greater LV ejection fraction (LVEF) (25% ± 6% vs. 37% ± 8%), and reduced LV end-systolic volume (LVESV) (174 ± 57 ml vs. 137 ± 37 ml).

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In this issue of *JACC: Heart Failure*, Zipes et al. (22) report the results of the long-awaited DEFEAT-HF (Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure) trial. In an elegant, single-blind RCT enrolling participants at 24 centers in the United States, Canada, Europe, and South America, patients were randomized to SCS-on versus SCS-off in a 3:2 fashion. Patients with a narrow QRS interval (<120 ms), LVEF ≤35%, and NYHA functional class III HF were eligible. Although originally powered to detect a 12.5% reduction in LVESV index (LVESVi) with a target population of 195 patients, the trial was plagued by slow enrollment and closed at 3 years with only 66 patients receiving devices. Overall patient demographic characteristics were comparable to those of early ICD trials, with ~79% of the subjects being male with an average age of 61 ± 12 years and LVEF of 29 ± 5%. Just over one-half of the patients had a history of ischemic cardiomyopathy with HF hospitalization in the 6 months before enrollment. Implantation was successful in all 66 patients who were randomized. System- or procedure-related complications were observed in 16.7%; lead dislodgment, fracture, device hematoma, and implant-related HF decompensation were the most common events and could be managed periprocedurally.

In contrast to the SCS Heart study, the primary endpoint of change in LVESVi was not significantly improved by SCS therapy in the DEFEAT-HF trial. Indeed, patients randomized to SCS-on tended to fare worse than their counterparts in SCS-off (38% vs. 70% showing a reduction in LVESVi). Secondary endpoints of change in peak Vo_2 and N-terminal pro-B-type natriuretic peptide were also not significantly different between the 2 groups. Additional secondary clinical endpoints of time to first HF hospitalization or death at 6 months, the Minnesota Living With Heart Failure Questionnaire score, change in NYHA functional class, and change in 6-min walk test were not different between SCS-on and SCS-off subjects. Also, there were no differences in arrhythmic (ventricular or atrial) burden, and no specific subgroup of patients was observed to benefit from SCS.

Zipes et al. (22) should be applauded for pressure-testing the theory of SCS and neuromodulation in humans with a clearly designed RCT. The findings of the DEFEAT-HF trial are discordant with those of SCS Heart study, but perhaps with good cause. Fundamental differences in surgical technique and mode of SCS delivery were present in the 2 trials. The SCS Heart study used two 8-electrode stimulation leads in the epidural space positioned to encompass the T1-3 level, whereas the DEFEAT-HF trial used a single 8-electrode lead that was placed lower at the T2-4 level. Of note, previous work has shown that SCS delivered at the T4 level demonstrates a greater antiarrhythmic effect (16), whereas that at the T1 level is associated with a heightened vagal tone (14).

Beyond differences in the study design and anatomic site of stimulation, the duty cycles of the devices in the 2 trials were also notably distinct. Stimulators in the SCS Heart study were programmed to deliver continuous therapy 24 h/day at 50 Hz and a pulse width of 200 μs, whereas stimulation in the DEFEAT-HF trial was 12 h/day based on individual sleep/wake cycles. Both studies titrated energy delivery to at least 90% of the maximal tolerated threshold, with the SCS Heart study allowing up to 110% of threshold. Although the difference in outcome between the 2 studies might indicate that "more is better," this type of reductive reasoning could be misleading. Before these studies were initiated in humans, both approaches were supported by preclinical work. Although continuous SCS has been associated with greater myocardium norepinephrine spillover in porcine models of ischemic heart failure (19), intermittent therapy on the whole appeared to demonstrate similar results with less risk of disabling paresthesia and fatigability (23). "Dose" finding, typically investigated within the realm of phase II studies, is sorely needed for new device technologies. This is especially salient of studies modulating autonomic tone, where there is so much inter-individual variability.

The results of the DEFEAT-HF trial are at once humbling and motivating—they raise more questions than answers about the mechanics of the neurohormonal system. Beyond anatomic location, what nexus point should be targeted for improved cardiovascular homeostasis? Is the dorsal column of the spinal cord appropriate for cardiac regulation? If it is, how do we individualize therapy for each patient? Is there a surrogate for autonomic tone (e.g., heart rate variability or muscle sympathetic nerve activity) that can be used to adjust therapeutic dose real time? Is there a phenotypic signature for response that we can use to select patients? Like other trials in the arena of neuromodulation, the technology has gotten ahead of our understanding of the physiology. Investigators pursuing device-based modulation of the autonomic system need to go back to the drawing board and

further the understanding of appropriate patient selection, autonomic tone surrogates, and suitable delivery of therapy. Although the DEFEAT-HF trial may have been a battle lost, it is invariably the lessons learned from defeat that serve as the foundation for future victories.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jagmeet Singh, Cardiology Division, Harvard Medical School, Massachusetts General Hospital Heart Center, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: jsingh@mgh.harvard.edu.

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KEY WORDS clinical trial results, heart failure, spinal cord stimulation