Title

Interventional and Device-based Autonomic Modulation in Heart Failure

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Abstract/Summary

Heart failure is an increasingly prevalent disease with high mortality and public health burden. It is associated with autonomic imbalance characterized by sympathetic hyperactivity and parasympathetic hypoactivity. Evolving novel interventional and device-based therapy has sought to restore autonomic balance by neuromodulation. Results of preclinical animal studies and early clinical trials have demonstrated its safety and efficacy in heart failure. In this review article, we will discuss specific neuromodulatory treatment modalities individually—spinal cord stimulation, vagus nerve stimulation, baroreceptor activation therapy and renal sympathetic nerve denervation.

Key Points (3–5)

- Heart failure (HF) is a disease categorized by sympathetic hyperactivity, parasympathetic withdrawal and impaired baroreflex control of sympathetic activation.
- Several measures of autonomic modulation either by implanted devices or interventions seek to restore the autonomic balance in HF and improve outcomes. These measures include spinal cord stimulation, vagus nerve

stimulation, baroreceptor activation therapy and renal sympathetic nerve denervation.

- Preclinical work and the majority of early clinical trials demonstrate the benefits of these modalities in HF. Additional larger, well-designed, outcome-based clinical trials are warranted to verify the results and determine whether these evolving, innovative neuromodulation approaches can be recommended to the growing population of HF patients.

Introduction

Congestive heart failure (HF), a disease with high mortality and increasing prevalence,[1] is characterized by autonomic imbalance, including decreased parasympathetic tone,[2, 3] hyperactive sympathetic tone[4, 5] and impaired baroreflex control of sympathetic activity.[6, 7] Pharmacotherapy attempting to restore the autonomic imbalance with drugs such as beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and aldosterone receptor antagonists have been shown to improve survival among HF patients and are recommended for HF patients with reduced ejection fraction.[1] However, the daunting prospect of HF burden and lack of recent breakthroughs in pharmacotherapy have led to the investigations of non-pharmacological approaches that can favorably modulate the autonomic tone.[8-11] In this article, we will discuss the latest avenues of research and clinical trials regarding the application of interventional or device-based approaches in treating HF through modulating autonomic activity—specifically, spinal cord stimulation (SCS), vagus nerve stimulation (VNS), baroreflex activation therapy (BAT) and renal sympathetic nerve denervation (RSDN).

Spinal Cord Stimulation

Technical Aspects

SCS has been used clinically for chronic pain (approved by the FDA in the US), peripheral vascular disease and refractory angina (in Europe). The procedure involves the subcutaneous placement of an epidural stimulation lead with distal poles at the level of T_2-T_4, which is connected to an implanted pulse generator in the para-spinal lumbar region (**Figure 1**). SCS can be applied at 90% of the motor threshold at a frequency of 50 Hz and a pulse width of 200 ms for 2 hours at a time, three times a day. It can also be applied for longer intervals.

Preclinical Research

Olgin *et al.* demonstrated that SCS at the level of T_1-T_2 increased the sinus cycle length and prolonged AV nodal conduction. These effects were abolished after transection of bilateral cervical vagus nerves but not transection of ansae subclaviae (sympathectomy), suggesting the effect of SCS is vagally mediated.[12] In a canine model of ischemic HF, SCS during transient myocardial ischemia reduced the incidence of spontaneous ventricular tachyarrhythmias.[13] This antiarrhythmic effect was again associated with vagal effects – reduction in sinus rate, prolongation of PR interval and lowering of blood pressure. With direct nerve recordings in ambulatory dogs, Garlie *et al.*[14] demonstrated that SCS attenuated augmented sympathetic activity from the stellate ganglion following myocardial infarction and pacing-induced HF in an animal model similar to the one noted below.

The chronic cardio-protective effect of SCS in HF was best demonstrated by a canine study[15] from the same investigator group. All canines first underwent foam embolization of the left anterior descending artery followed by ventricular tachypacing to create an ischemic HF model. Then the animals were equally randomized to 4 groups:

- SCS (T_4 level, 90% motor threshold, 50 Hz, 0.2-ms pulse duration, 2 hours at a time, three times daily).
- Medical therapy (carvedilol + ramipril).
- Combined SCS and medical therapy.
- Control group.

The dogs were followed chronically for 10 weeks. A significant decline in serum norepinephrine and brain natriuretic peptide levels along with decrease of ischemic ventricular tachyarrhythmias was observed in dogs receiving SCS. Most interestingly,

dogs receiving SCS (with or without medical therapy) had greatest improvement of LVEF (from 17% to 52%) with reductions in ventricular volume. The improvement persisted throughout the treatment period.

Clinical Trials

Based on the preclinical work, a number of clinical studies sought to assess the efficacy and safety of SCS in systolic HF patients (**Table 1**).[16-19] Of those trials the largest is DEFEAT-HF with implanted PrimeAdvanced neurostimulator (Medtronic Inc, Minneapolis, MN, USA). It is a multicenter, prospective, randomized (3:2 fashion) control trial enrolling 66 patients with LVEF ≤ 35%, NYHA class III HF symptoms while on optimal medical therapy, narrow QRS duration and a dilated LV.[17] The preliminary data of six months of follow-up will soon be presented at the 2014 American Heart Association scientific sessions. The results of a smaller prospective trial that enrolled nine patients with LVEF ≤ 30% and NYHA class III HF symptoms while on optimal medical therapy have been published.[16] During the 7-month period of follow up, five patients had improved symptoms by at least one NYHA class and three were unchanged, while no one worsened. Despite the small sample size, this study demonstrated the safety and feasibility of SCS in patients with advanced HF. In particular, SCS did not affect the functions (sensing, detection and therapy delivery) of the implantable cardioverter defibrillator.

Vagus Nerve Stimulation

Technical Aspects

Chronic VNS has been used clinically for years for refractory epilepsy and depression.[20] Its use in HF has recently been studied during right cervical VNS. A cuff electrode is secured around the vagus about 3 cm below the carotid artery bifurcation. A brief

stimulation that reduces heart rate by 10% is performed to ensure the correct positioning. The stimulation lead is then tunneled under the skin and over the clavicle to join the intracardiac sensing electrode (placed in the right ventricle, to prevent excessive bradycardia) and the pulse generator in the subcutaneous pocket in the right subclavicular region (**Figure 2**). The stimulation parameter then follows an up-titration protocol to achieve heart rate reduction of 5-10 beats/min without eliciting adverse reactions.[21, 22]

Preclinical Research

While HF is associated with a decreased vagal activity, decreased vagal activity itself is associated with higher mortality among HF patients.[23] VNS is thus an attractive idea in treating HF. A number of animal studies using rats and dogs have shown that chronic VNS improved LV hemodynamics[24, 25] and, more importantly, improved survival in HF.[26] With an implanted device to continuously record autonomic nerve activity in ambulatory canines, Shen *et al.*[27] observed that chronic VNS led to a significant reduction in sympathetic activity from the left stellate ganglion, which may underlie the cardio-protective property of VNS. Besides, VNS has additional beneficial effects:

- VNS has been shown to attenuate systemic inflammation.[25, 28]
- VNS, via the modulation of nitric oxide,[29] may reduce the slope of action potential duration restitution curve,[30] which is important in the initiation of VF.[31]
- VNS can also significantly increase the expression of connexin-43,[24] which is down-regulated in failing human hearts and thereby arrhythmogenic.[32]
- VNS has been demonstrated to be associated with its prevention of mitochondrial dysfunction during ischemia-reperfusion.[33]

Clinical Trials

In a recent multi-center, single-arm, open-label pilot study enrolling 32 patients with NYHA class II-IV symptoms and LVEF ≤ 35% using Cardiofit system (BioControl Medical Ltd, Yehudi, Israel), VNS was found to be safe and tolerable and to improve quality of life and LV systolic function.[22] The positive result has prompted larger randomized trials to examine the efficacy and safety of this treatment modality in patients with severe systolic HF (**Table 2**).[34-36] The results of two of these trials were recently presented in the European Society of Cardiology Congress 2014 and showed conflicting findings.

- NECTAR-HF is a prospective, double-blinded, randomized control study that enrolled 96 patients with NYHA class II-III symptoms and LVEF ≤ 35% and evaluated right-sided VNS. It failed to demonstrate an improvement in LV end-systolic diameter, the primary endpoint, in 6 months' time.[37] However, it did show that VNS was safe and able to significantly improve the quality of life.
- Anthem-HF is a prospective, open-label, randomized control study that enrolled 60 patients with NYHA class II-III symptoms and LVEF ≤ 40% and evaluated both right-sided and left-sided VNS. It showed that either right-sided or left-sided VNS was able to significantly improve LVEF and reduce LV end-systolic diameter in 6 months' time.[38]

The reason for such obvious different results is unclear. One possibility is that different types of stimulating protocols and/or equipment utilized in two studies may have recruited different types of fibers within the cervical vagus nerve. In fact, cervical vagus nerves invariably contain a small percentage of sympathetic nerves.[39, 40] Stimulating the cervical vagus is actually stimulating a vagosympathetic trunk. Whether that reduces the beneficial effects of cervical VNS remains to be determined. Another larger trial, INOVATE-HF, with a plan to enroll 650 patients with similar baseline parameters (LVEF ≤ 40%, NYHA class III symptoms and a dilated LV) is ongoing.[34] The results of this trial

may determine whether VNS is really beneficial in HF. Of note, INOVATE-HF is the only trial of VNS that chose all-cause mortality or unplanned HF hospitalization as the primary outcome measure.

Baroreceptor Activation Therapy

Technical Aspects

Chronic electrical activation of the carotid baroreflex, known as BAT, has been commercially available and tested in patients with resistant hypertension.[41, 42] It has since been investigated in HF. For the traditional Rheos system (CVRx Inc, Minneapolis, MN, USA), the implantation involves surgically exposing both carotid sinuses and placing electrodes around the carotid adventitial surface bilaterally. The leads are subcutaneously tunneled and connected to an implantable stimulation device placed in the subclavian subcutaneous position on the anterior chest wall. The newer generation (Barostim neo, also from CVRx Inc) has only one carotid sinus electrode with smaller size (**Figure 3**) that delivers less power and thus allows easier implant and less adverse effects.

Preclinical Research

Normally, activation of the baroreceptors within the carotid sinuses by an increase in aortic pressure or volume sends impulses to the medulla that lead to restoration of pressure homeostasis by decreasing efferent sympathetic activity while increasing efferent parasympathetic activity,[43] both desirable in HF. Furthermore, defective baroreflex control of the heart rate in the failing heart has long been recognized.[44] Therefore, BAT has the potential to benefit HF patients and has been studied in an experimental HF model. In a microembolization canine model of HF, chronic BAT significantly increased LV systolic function and reduced plasma norepinephrine.[45] In

another study using rapid pacing model of HF, chronic BAT reduced LV filling pressure, decreased plasma norepinephrine and doubled survival duration.[46]

Clinical Trials

A recent single-center, open-label, single-arm study enrolled eleven patients with LVEF ≤ 40% and NYHA class III HF symptoms while on optimal medical therapy that received BAT for 6 months.[47] Chronic BAT was associated with significant improvement in baroreflex sensitivity, LVEF, NYHA class, quality of life and 6-min walk distance, along with significant decrease in muscle sympathetic activity. Larger clinical trials are ongoing[48-50] and summarized in **Table 3**. Of note, the Rheos HOPE4HF trial[48] is one of few trials of new treatment modalities evaluating HF with preserved ejection fraction (or diastolic HF, LVEF ≥ 40%) population.[51]

Renal Sympathetic Nerve Denervation

Technical Aspects

Catheter-based RSDN is most widely applied clinically as a treatment for resistant hypertension.[52, 53] Beyond blood pressure, RSDN may prove beneficial in other diseases associated with sympathetic hyperactivity, including HF.[54] Prior to the procedure, careful evaluation by imaging of the renal artery anatomy along with renal function tests is warranted to assess suitability of the intervention.[55] Via a standard femoral artery access, a flexible endovascular electrode catheter connected to a generator is placed within the renal arteries to allow delivery of radiofrequency energy. A series of lesions along each renal artery then are delivered to disrupt the renal nerves located in the adventitia of the renal arteries. For safety reasons, each lesion should be at least 5 mm apart.

Preclinical Research

RSDN ablates both efferent and afferent renal sympathetic nerves as they run together, with higher nerve density in the proximal segments and ventral region.[56] By ablating the efferent nerves, RSDN decreases the renal norepinephrine spillover by 47%[57] and attenuates the activity of renin-angiotensin-aldosterone system,[58] both important in the pathogenesis of LV remodeling in HF. More importantly from a cardiac standpoint, afferent RSDN leads to decreased feedback activation to the central nervous system and thereby decreased sympathetic input to the heart (**Figure 4**). In a murine model of ischemic HF, RSDN is associated with reduced LV filling pressure and improved LVEF after 4 weeks of follow up.[59] Among patients with resistant hypertension, RSDN leads to a reduction in heart rate and atrioventricular conduction,[60] and, in another study, reduction of LV mass, reduction of LV filling pressure, shortening of isovolumic relaxation time and increase of LVEF.[61]

Clinical Trials

The first trial examining the safety of RSDN in HF patients is REACH-Pilot trial.[62] In the seven patients with chronic systolic HF and normotension prior to the procedure, there were no hypotensive or syncopal events over a 6-month follow-up period. The renal function remained stable. Although limited in size, the pilot study showed that there was a trend towards an improvement in symptoms and exercise capacity. The encouraging results call for larger randomized trials to validate the efficacy and safety of this modality in HF, despite the failure of a recent prospective, randomized, blinded study (SIMPLICITY HTN-3) to demonstrate any benefit of RSDN in patients with resistant hypertension.[63] Several larger ongoing trials[64-68] are summarized in **Table 4**.

Evolving technology

Recent preclinical work from the Cleveland Clinic demonstrated that epivascular[69] and, more excitingly, endovascular[70] cardiac plexus stimulation can increase LV contractility without increasing heart rate. This was achieved by stimulating the cardiac plexus between the ascending aorta and right pulmonary artery. It is known that cardiac ganglionated plexi concentrated in epicardial fat pads play a cardinal role in coordinating complex interactions between extrinsic and intrinsic cardiac autonomic nervous system[71] and contain highly co-localized sympathetic and parasympathetic ganglion cells.[72, 73] The idea that stimulating cardiac plexus endovascularly can improve LV contractility is fascinating, given that the technique is simple, requiring the placement of a stimulation catheter in the right pulmonary artery similar to that of a Swan-Ganz catheter. In addition, chronic stimulation of the cardiac plexus may help restore the impaired endogenous nerve activity from the plexus in HF.[74]

Summary

HF is increasingly common and remains deadly, despite guideline-based optimal medical therapy.[1] Most currently available interventional and device-based treatment modalities for HF (defibrillator, ventricular assist device or heart transplantation) are often “fallbacks” instead of disease-modifiers. The new modalities discussed in the present article – SCS, VNS, BAT and RSDN, however, have several distinct features:

- They seek to correct one of the fundamental impairments of HF – autonomic imbalance, which may underpin the survival benefits of beta-blockade and inhibition of renin-angiotensin-aldosterone system. One must remember, however, that beta-blockade is just blockade of beta receptors. That leaves alpha receptors unaffected (except perhaps with carvedilol), and does not capitalize on all the other benefits of device-based neuromodulation.

- Through the same neuromodulation mechanisms, they help prevent the occurrence of ventricular tachyarrhythmias,[75] which remain a common cause of death in HF populations.
- Unlike previous device-based therapy such as implantable cardioverter defibrillator or cardiac resynchronization therapy that focus on HF with reduced ejection fraction, some of the ongoing trials with new modalities (Rheos HOPE4HF for BAT, DIASTOLE, RDT-PEF and RESPECT-HF for RSDN) enroll patients with HF with preserved EF, a population that continues to grow and may overtake HF with reduced EF in the near future.[76]
- An attractive feature of these new modalities is that they are not "new" to the medical practice and have been applied to other indications for years. Their application for a new indication therefore should be easier and safer.

Nonetheless, caution should be exercised when examining the ongoing trials of new modalities for HF. In addition to the inherent difficulty of ensuring "true double-blindness" of these interventional and device-based treatment modalities, a major criticism is that the majority of the completed and ongoing trials have used "soft endpoints" such as changes in echocardiographic findings or peri-procedural safety issues rather than "hard endpoints" such as cardiovascular mortality or HF event that requires hospitalization. Furthermore, as MOXCON trial demonstrated, moxonidine, an antihypertensive agent, despite reducing central sympathetic nerve activity and circulating norepinephrine concentrations, caused excessive mortality in HF patients and led to early termination of the trial.[77] This suggests that generalized sympathetic inhibition in HF may be harmful. In contrast, results of completed trials of the new modalities have so far been encouraging. The mechanisms of neuromodulation of these new modalities are perhaps more complex and not just anti-sympathetic. Altogether, autonomic modulation through interventions and devices in HF looks promising. It remains to be seen whether these

new modalities can be recommended to ever growing population of HF patients pending results from larger randomized trials and further investigations.

Trial	N	Criteria	Design	Endpoint*	Status#
Neurostimulation of Spinal Nerves That Affect the Heart	9	• LVEF ≤ 30% • NYHA III	Randomized, double-blind, crossover	Safety, device interactions, symptoms	Results published (see text)
DEFEAT-HF	66	• LVEF ≤ 35% • NYHA III • Narrow QRS • Dilated LV	Randomized, single-blind, parallel	Δ in LV volume	Active, not recruiting. Prelim result soon be presented.
SCS HEART	20	• LVEF 20-35% • NYHA III-IV • Dilated LV	Single-arm, open label	Safety, Δ in LV function, exercise capacity, QoL	Recruiting
TAME-HF	20	• LVEF ≤ 35% • NYHA III • Narrow QRS	Single-arm, open label	Δ in LV volume, symptoms, exercise capacity	Recruiting

Table 1. Clinical trials of Spinal Cord Stimulation in Heart Failure. Abbreviations: DEFEAT-HF, Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure; SCS HEART, Spinal Cord Stimulation For Heart Failure; TAME-HF, Trial of Autonomic neuroModulation for trEatment of Chronic Heart Failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; QoL, quality of life. * Only primary outcome measures listed. # As of October 2014.

Trial	N	Criteria	Design	Endpoint*	Status#
CardioFit™ for the Treatment of Heart Failure	32	• LVEF ≤ 35% • NYHA II-IV	Single-arm, open label	All adverse events	Results published (see text)
INOVATE-HF	650	• LVEF ≤ 40% • NYHA III • Dilated LV	Randomized, open label, parallel	All-cause mortality or unplanned HF hospitalization	Recruiting
NECTAR-HF	96	• LVEF ≤ 35% • NYHA II-III • Dilated LV	Randomized, double-blind, crossover	Δ in LV volume, all-cause mortality	Results published (see text)
ANTHEM-HF†	60	• LVEF ≤ 40% • NYHA II-III • Dilated LV	Randomized, open label, parallel	Δ in LV functions, adverse events	Results presented (see text)

Table 2. Clinical trials of Vagus Nerve Stimulation in Heart Failure. Abbreviations: INOVATE-HF, INcrease Of VAgal TonE in CHF; NECTAR-HF, Neural Cardiac Therapy for Heart Failure Study; ANTHEM-HF, Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure. * Only primary outcome measures listed. # As of October 2014. † Also test left-sided VNS.

Trial	N	Criteria	Design	Endpoint*	Status#
The study by Gronda et al. from Italy	11	• LVEF ≤ 40% • NYHA III	Single-arm, open label	Δ in muscle sympathetic activity	Completed. Results published (see text)
Rheos HOPE4HF	540	• LVEF ≥ 40% • Symptomatic • Hypertensive	Randomized, open label, parallel	CV death or HF event, all adverse events	Active, not recruiting
XR-1 Randomized Heart Failure study	150	• LVEF ≤ 35% • NYHA III	Randomized, open label, parallel	Δ in LVEF	Active, not recruiting
Barostim HOPE4HF	60	• LVEF ≤ 35% • NYHA III	Randomized, open label, parallel	Δ in HF metric, all adverse events	Active, not recruiting

Table 3. Clinical trials of Baroreflex Activation Therapy in Heart Failure. * Only primary outcome measures listed. # As of October 2014.

Trial	N	Criteria	Design	Endpoint*	Status#
REACH-Pilot	7	• Chronic HF • NYHA III-IV	Single-arm, open label	Safety study	Completed. (see text)
SymplicityHF	40	• LVEF < 40% • NYHA II-III • GFR 30-75	Single-arm, open label	Safety study	Recruiting
Renal Denervation in Patients With Chronic Heart Failure	100	• LVEF10-40% • NYHA II-III • GFR > 30	Randomized, open label, parallel	Safety, number of comliplications	Not yet recruiting
DIASTOLE	60	• HF symptoms • LVEF ≥ 50% • Evidence of HFpEF • HTN • GFR > 30	Randomized, open label, parallel	Change in E/E'	Recruiting
RDT-PEF	40	• LVEF > 40% • NYHA II-III • Evidence of HFpEF	Randomized, open label, parallel	Change in symptoms and echo findings	Recruiting
RESPECT-HF	144	• LVEF ≥ 50% • NYHA II-IV • Evidence of HFpEF • Episode of ADHF	Randomized, open label, parallel	Change in LA volume index	Recruiting

Table 4. Clinical trials of Renal Sympathetic Nerve Denervation in Heart Failure.

Abbreviations: REACH-Pilot, Renal Artery Denervation in Chronic Heart Failure; SymplicityHF, Renal Denervation in Patients With Chronic Heart Failure & Renal Impairment Clinical Trial; DIASTOLE, Denervation of the renAl sympathetIc nerveS in hearT Failure With nOrmal Lv Ejection Fraction; RDT-PEF, Renal Denervation in Heart Failure With Preserved Ejection Fraction; RESPECT-HF, Renal Denervation in Heart Failure Patients With Preserved Ejection Fraction. * Only primary outcome measures listed. # As of October 2014.

Figure Legends

Figure 1. Spinal Cord Stimulation (SCS). A. Schematic representation of SCS system. B. X-ray image showing the placement of the SCS lead with concurrent cardiac resynchronization therapy-defibrillator (CRT-D) device and leads. (From Torre-Amione G, Alo K, Estep JD, et al. Spinal cord stimulation is safe and feasible in patients with advanced heart failure: early clinical experience. Eur J Heart Fail 2014;16(7):788-795; with permission.)

Figure 2. Vagus Nerve Stimulation (VNS). A. Schematic representation of VNS system. (From Schwartz PJ, De Ferrari GM, Sanzo A, et al. Long term vagal stimulation in patients with advanced heart failure: first experience in man. Eur J Heart Fail 2008;10(9):884-891; with permission.) B. X-ray image showing the placement of the VNS stimulator with a previously implanted implantable cardioverter defibrillator (ICD). (From Singh JP, Kandala J, Camm AJ. Non-pharmacological modulation of the autonomic tone to treat heart failure. Eur Heart J 2014;35(2):77-85; with permission.)

Figure 3. Baroreceptor Activation Therapy (BAT). A. Schematic representation of BAT system. The new generation, Barostim neo, is shown here with one carotid sinus nerve stimulator (Panel B) that carries one electrode connected to the patch electrode (Panel C) that will be fixed to the carotid sinus nerve. (From Kuck KH, Bordachar P, Borggrefe M, et al. New devices in heart failure: an European Heart Rhythm Association report: developed by the European Heart Rhythm Association; endorsed by the Heart Failure Association. Europace 2014;16(1):109-128; with permission.)

Figure 4. Renal Sympathetic Nerve Denervation (RSDN). Physiological and pathophysiological actions of renal sympathetic afferent and efferent nerves can be

blocked by RSDN. (From Krum H, Sobotka P, Mahfoud F, et al. Device-based antihypertensive therapy: therapeutic modulation of the autonomic nervous system. Circulation 2011;123(2):209-215; with permission.)

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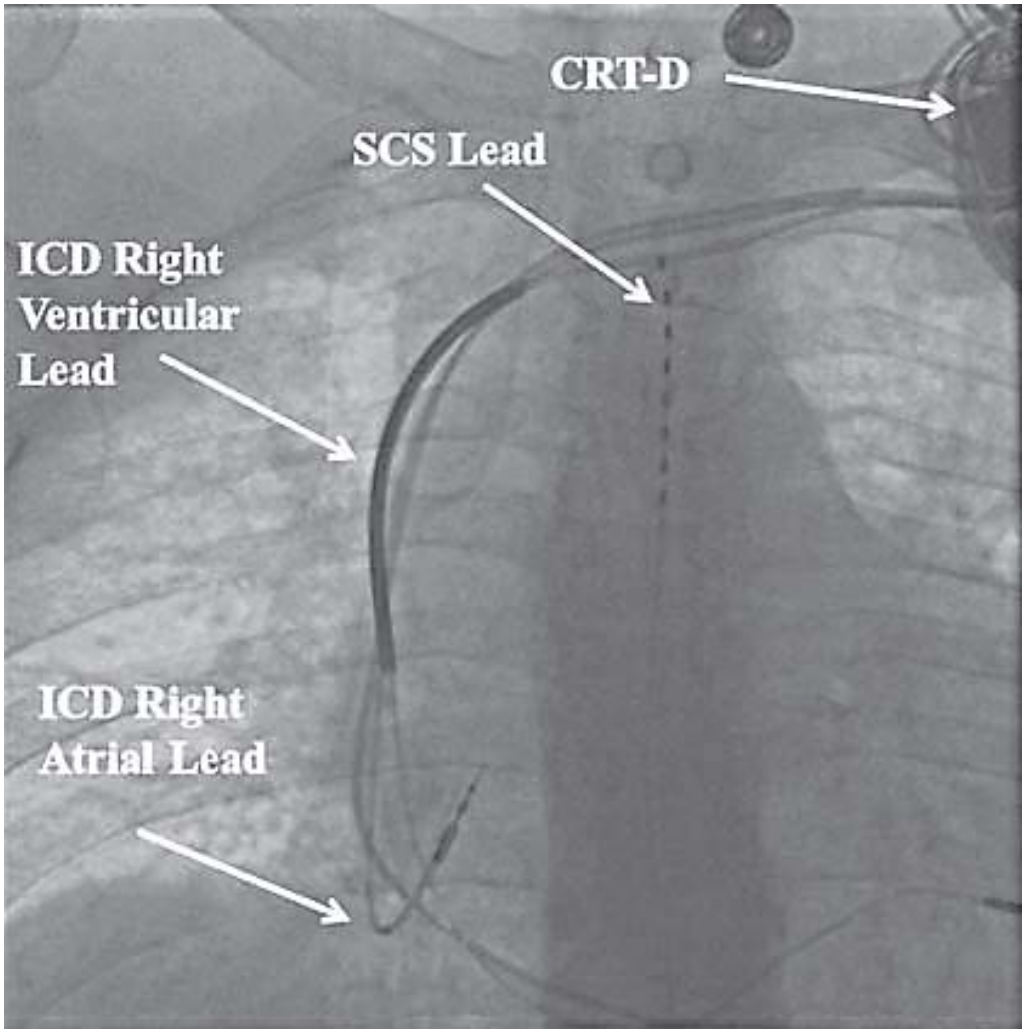
A

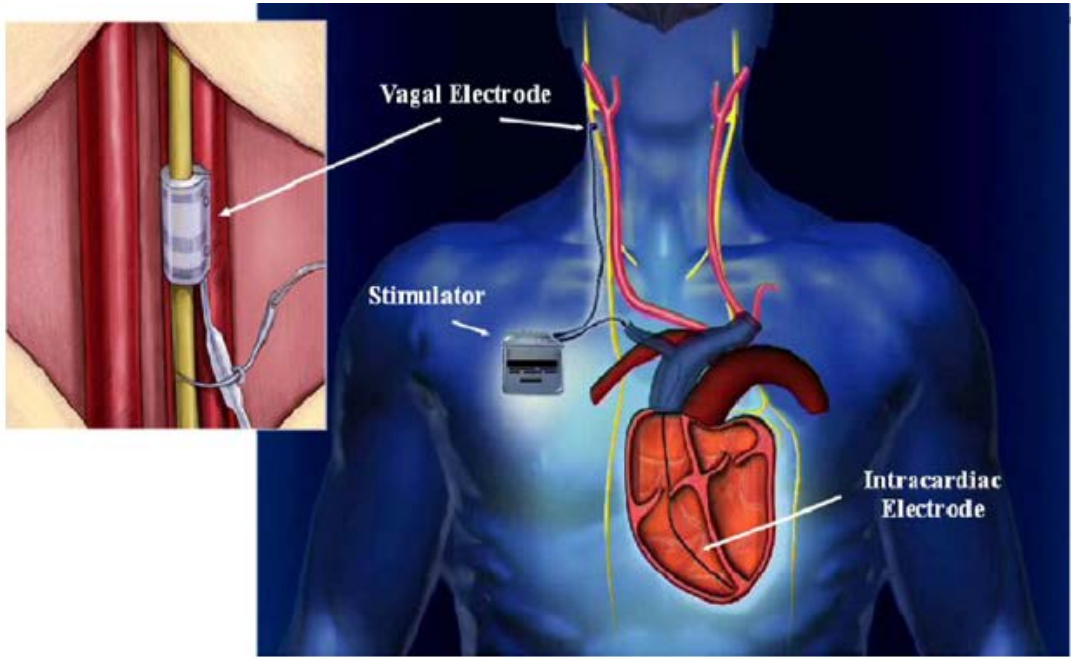

Leads
at T_2-T_4
Pulse
generator

B

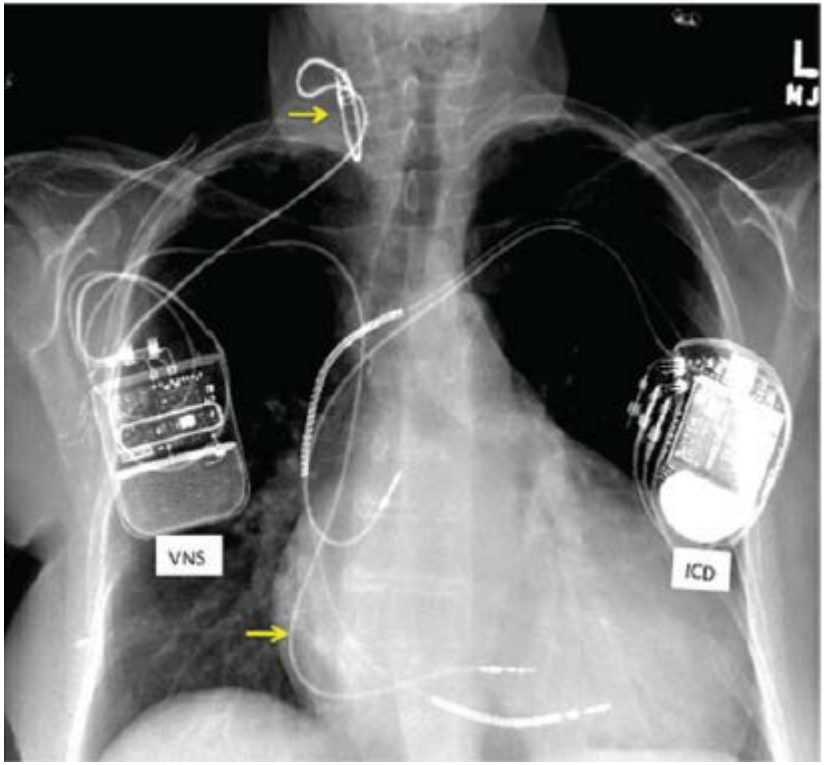

CRT-D
SCS Lead
ICD Right
Ventricular
Lead
ICD Right
Atrial Lead

Trial	N	Criteria	Design	Endpoint*	Status#
Neurostimulation of Spinal Nerves That Affect the Heart	9	• LVEF ≤ 30% • NYHA III	Randomized, double-blind, crossover	Safety, device interactions, symptoms	Results published (see text)
DEFEAT-HF	66	• LVEF ≤ 35% • NYHA III • Narrow QRS • Dilated LV	Randomized, single-blind, parallel	Δ in LV volume	Active, not recruiting. Prelim result soon be presented.
SCS HEART	20	• LVEF 20-35% • NYHA III-IV • Dilated LV	Single-arm, open label	Safety, Δ in LV function, exercise capacity, QoL	Recruiting
TAME-HF	20	• LVEF ≤ 35% • NYHA III • Narrow QRS	Single-arm, open label	Δ in LV volume, symptoms, exercise capacity	Recruiting

A

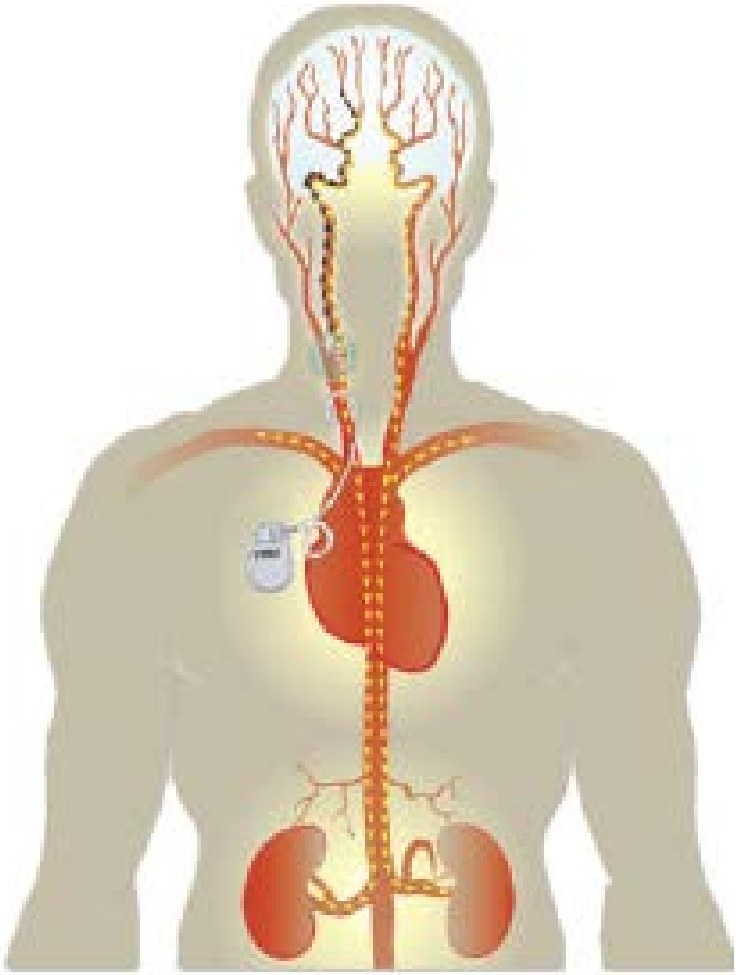

Vagal Electrode
Stimulator
Intracardiac Electrode

B


VNS
ICD

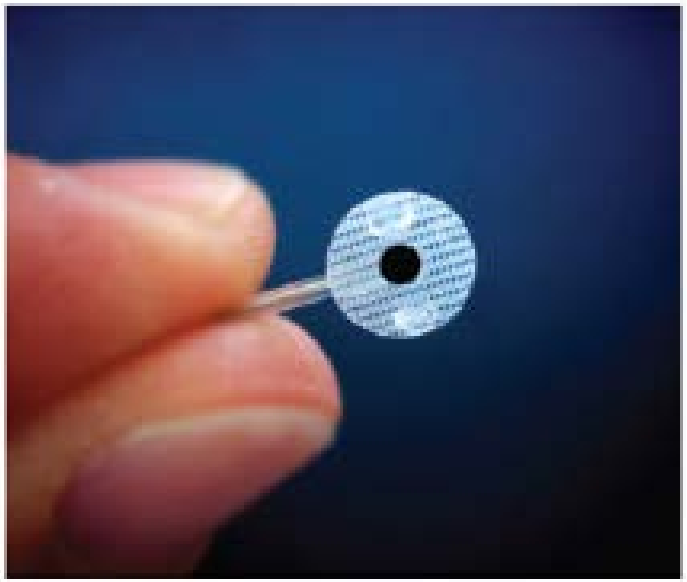
Trial	N	Criteria	Design	Endpoint*	Status#
CardioFit™ for the Treatment of Heart Failure	32	• LVEF ≤ 35% • NYHA II-IV	Single-arm, open label	All adverse events	Results published (see text)
INOVATE-HF	650	• LVEF ≤ 40% • NYHA III • Dilated LV	Randomized, open label, parallel	All-cause mortality or unplanned HF hospitalization	Recruiting
NECTAR-HF	96	• LVEF ≤ 35% • NYHA II-III • Dilated LV	Randomized, double-blind, crossover	Δ in LV volume, all-cause mortality	Results published (see text)
ANTHEM-HF†	60	• LVEF ≤ 40% • NYHA II-III • Dilated LV	Randomized, open label, parallel	Δ in LV functions, adverse events	Results presented (see text)

A

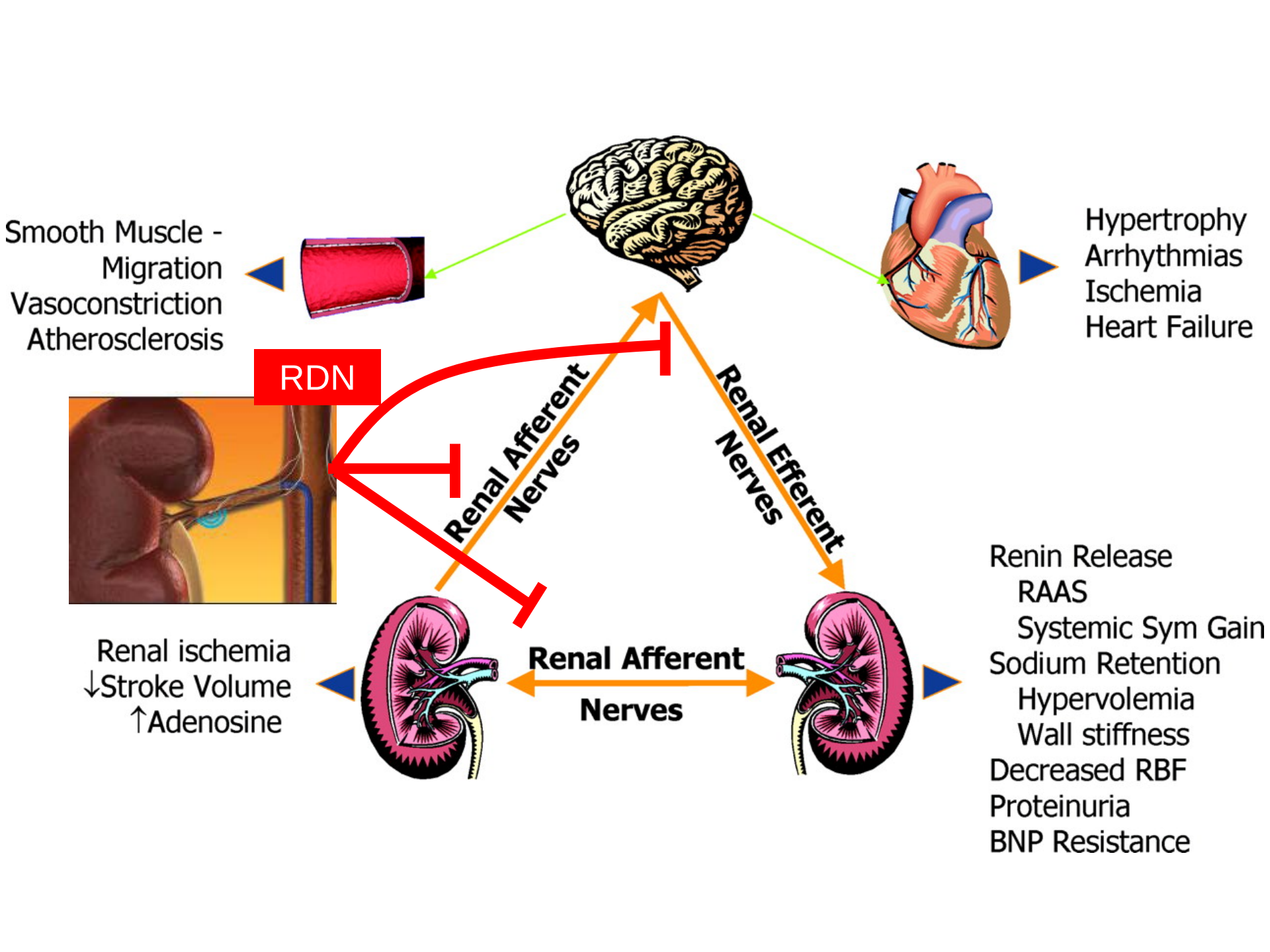


B

C



Trial	N	Criteria	Design	Endpoint*	Status#
The study by Gronda et al. from Italy	11	• LVEF ≤ 40% • NYHA III	Single-arm, open label	Δ in muscle sympathetic activity	Completed . Results published (see text)
Rheos HOPE4HF	540	• LVEF ≥ 40% • Symptomatic • Hypertensive	Randomized, open label, parallel	CV death or HF event, all adverse events	Active, not recruiting
XR-1 Randomized Heart Failure study	150	• LVEF ≤ 35% • NYHA III	Randomized, open label, parallel	Δ in LVEF	Active, not recruiting
Barostim HOPE4HF	60	• LVEF ≤ 35% • NYHA III	Randomized, open label, parallel	Δ in HF metric, all adverse events	Active, not recruiting


Smooth Muscle -
Migration
Vasoconstriction
Atherosclerosis
Hypertrophy
Arrhythmias
Ischemia
Heart Failure
RDN
Renal Afferent Nerves
Renal Efferent Nerves
Renal ischemia
↓Stroke Volume
↑Adenosine
Renal Afferent
Nerves
Renin Release
RAAS
Systemic Sym Gain
Sodium Retention
Hypervolemia
Wall stiffness
Decreased RBF
Proteinuria
BNP Resistance

Trial	N	Criteria	Design	Endpoint*	Status#
REACH-Pilot	7	• Chronic HF • NYHA III-IV	Single-arm, open label	Safety study	Completed. (see text)
SymplicityHF	40	• LVEF < 40% • NYHA II-III • GFR 30-75	Single-arm, open label	Safety study	Recruiting
Renal Denervation in Patients With Chronic Heart Failure	100	• LVEF10-40% • NYHA II-III • GFR > 30	Randomized, open label, parallel	Safety, number of comliplications	Not yet recruiting
DIASTOLE	60	• HF symptoms • LVEF ≥ 50% • Evidence of HFpEF • HTN • GFR > 30	Randomized, open label, parallel	Change in E/E'	Recruiting
RDT-PEF	40	• LVEF > 40% • NYHA II-III • Evidence of HFpEF	Randomized, open label, parallel	Change in symptoms and echo findings	Recruiting
RESPECT-HF	144	• LVEF ≥ 50% • NYHA II-IV • Evidence of HFpEF • Episode of ADHF	Randomized, open label, parallel	Change in LA volume index	Recruiting