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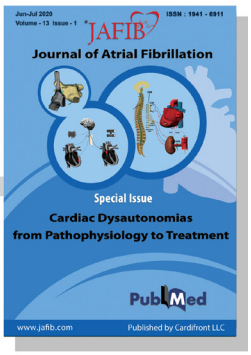

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Device Autonomic Regulation Therapy in Patients with Heart Failure and Reduced Ejection Fraction

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Abstract

Heart failure with reduced ejection fraction (HFrEF) is a common, incompletely treatable, complex, progressive, and severe medical problem despite guideline-directed medical therapy. HFrEF is associated with sympathetic activation and parasympathetic inhibition; these reflexive processes may ultimately be maladaptive and exacerbate or even perpetuate the problem. Attempts to regulate autonomic tone during HFrEF in animal models and in humans has shown promise with beneficial effects that include improvement in symptoms, mitigation of arrhythmic events, reduction in mortality, and correction in hemodynamics. Several modalities to regulate autonomic tone such as unilateral parasympathetic nerve activation, baroreceptor activation, renal nerve ablation and spinal cord stimulation have been investigated. Although they demonstrated some benefit, the long-term efficacy in HFrEF has not been proven. Considering specific limitations of each modality, to draw definitive conclusions is impossible at this time. Here, we review the present state-of-the-art literature? of device of autonomic regulation therapy to affect outcomes in HFrEF

Introduction

Heart failure (HF) with reduced ejection fraction (HFrEF) is a complex, progressive, debilitating, and life-threatening condition. Current guideline-directed therapy including β-adrenergic blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, nitrates combined with hydralazine, angiotensin receptor/neprilysin inhibitors, implantable cardioverter defibrillators, resynchronization devices, and myocardial revascularization is often not enough. Interest in non-pharmacologic therapeutic options, with the hope of further decreasing morbidity and mortality in patients with HFrEF has evolved. The autonomic nervous system (ANS) may play a compensatory, or even a harmful role, in HFrEF. Manipulation of the ANS, utilizing vagal nerve simulator (VNS), spinal cord stimulator (SCS), renal nerve ablation and baroreceptor activation therapy (BAT), has been studied. Here, we consider these autonomic regulation therapies used to improve outcomes in patients with HFrEF and review the present state of knowledge.

Pathophysiology of the Autonomic Nervous System in Heart Failure

In health, at rest, the parasympathetic nervous system exhibits dominant control over the cardiovascular system but, in patients with HFrEF, reflex resting sympathetic activation, often as a compensatory mechanism, with partial release of parasympathetic control, helps maintain cardiac output and improve hemodynamics[1]. However, therapy to counteract excess sympathetic activation is beneficial in HFrEF as is evident by benefits of β-adrenergic blocker therapy[2]. The complex and dynamic interrelationships between excess, often compensatory, sympathetic activation and parasympathetic inhibition on the severity of underlying initial hemodynamics and left ventricular dysfunction[3] cannot be underemphasized but the causal mechanism of the relationship to HF progression is not understood completely. Yet, greater sympathetic activation and parasympathetic inhibition is associated with poorer outcomes and greater hemodynamic compromise[1, 4, 5]. Similarly, there is disruption in baroreflex control that may be counterproductive[6]. Intervening upon these shifts from sympathetic dominance and towards parasympathetic stimulation has potential value even though these shifts may be counterintuitive from the hemodynamic perspective present during decompensated HF[7, 8].

The importance of preserved baseline parasympathetic activation and vagal reflexes in recent myocardial infarction was highlighted in the Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) trial[9]. In this prospective study of 1284 patients with preserved left ventricular function, heart-rate variability and baroreflex sensitivity were assessed. Baroreflex sensitivity was calculated based on heart rate and blood pressure responses to phenylephrine. The 2-year mortality was 17% in those with both low heart rate variability and low baroreflex activity versus 2% for those who had neither of these. Thus, patients who had excessive sympathetic activation were at greater risk of

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dying, and those with preserved parasympathetic tone and vagal reflexes had a better prognosis. Multivariate analysis showed that baroreflex sensitivity predicts cardiovascular mortality (p=0.0001). The relative risk for impaired baroreflex sensitivity was 11.4 (95% CI 3.3-39.0). The prediction was greatest for the patients younger than 65 (relative risk: 19.6; 95% CI 4.1-94.8) but was still substantial among patients older than 65 (relative risk: 7.2; 95% CI 1.3-39.9). Depressed baroreflex sensitivity predicted high mortality (18% vs 4.6%, p=0.01) in patients with ejection fractions <35%.

While this study was performed in patients with acute myocardial infarction, not specifically HFrEF, our current treatment methods and data supporting these treatments indicate the relationship of autonomic dysfunction and HF. Indeed, long-term sympathetic stimulation is associated with poorer prognosis[11]. Inhibition of the sympathetic nervous system by β-blockade improves outcomes, implying that tonic sympathetic activation and/or catecholamine excess is a cardiotoxic "double-edged sword"[12, 13]. Attempts to treat HFrEF with sympathomimetics or inotropes[14], including phosphodiesterase inhibitors (type 5)[15], calcium sensitizers[14], myosin activators[16], and adenosine-1 antagonists[17] have failed miserably. Despite initial enthusiasm, drugs that increase, or mimic, sympathetic activation[14, 16, 18] including dopamine[16], ibopamine[19], milrinone[20], amrinone[21], enoximone[16, 22], flosequinan[23], istaroxime, bosentan[22], vesnarinone[24] are uniformly harmful even if symptoms improve for a short time[25-27]. While initial inotropic and/or sympathetic stimulation may result in an acute hemodynamic advantage, long-term effects are damaging. The net effect of increasing heart rate (via β-1 receptors), contractility (via β-1 receptors), and peripheral vascular resistance (via ∝-1 receptors) in HF thus appears to be ultimately maladaptive. While these mechanisms initially increase cardiac output, maintain blood pressure, and maintain tissue perfusion, they increase myocardial oxygen demand, damage myocardium directly, trigger ventricular arrhythmias, and precipitate death. Norepinephrine is directly myopathic[11].

Loss of parasympathetic tone in HFrEF is part of the problem as well[7] as it causes a reflexive increase in sympathetic tone (the parasympathetic nervous system is a potent and rapid inhibitor of the sympathetic nervous system). However, parasympathetic activity has additional unique, complex, and integral functions independent of sympathetic activation. While parasympathetic activation predominantly slows heart rate, it also reduces ischemia and has antiarrhythmic effects[28-30]. The effects are complex and interwoven as parasympathetic stimulation (including, potentially afferent effects) corrects cell-to-cell conduction abnormalities[29] via connexin-[43] and gap junctions, affects nitric oxide synthase expression[31], is anti-inflammatory[32] by reducing cytokine release (TNF-∝, IL-1 β, IL-6 and IL-18 via ∝-7 nicotinic acetylcholine receptor stimulation) [7, 18 33], is antioxidant[31], enhances circulating mediators, beneficially affects remodeling by angiotensin II[34] and potentially affects vasopressin excess[35]. The Vagus nerve may also affect intracellular calcium handling, improve baroreflex sensitivity[36], increase capillary density, reduce apoptosis and decrease myocardial fibrosis to reverse deleterious cardiac remodeling[37]. Vagal modulation of heart rate may be valuable as faster resting sinus rates in HF patients, seen in the SHIFT[38] and in an implantable cardioverter defibrillator (ICD) population in the INTRINSIC RV[39] trial, are linked to deleterious outcomes. Autonomic modulation may have a role to provide further benefit after medical therapy including β-blockade[40] in HFrEF.

Therefore, in HFrEF, parasympathetic activation and sympathetic inhibition may improve ventricular function, reduce symptoms and improve survival. The interrelationships, however, with both limbs of the autonomic nervous system are difficult to modulate and are complex. Nicotinic ganglionic activation seems to be impaired in HF and seems to be one of the targets to improve vagal activation[41, 42]. However, multiple locations potentially responsible for impaired parasympathetic regulation that may be worth considering include vagal afferent modulation that also may affect vascular regulation and even affect the intrinsic autonomic nervous system[43]. Afferent stimulation has not been assessed completely but it is one of the key components responsible for the arterial baroreflex. In HFrEF, a major problem is thought to be decreased baroreceptor sensitivity leading to increased sympathetic activity. Afferent stimulation may be one of the targets, as it has been shown with use of tragus nerve stimulation[44]. The devices causing baroreceptor activation work via afferent activation.

The "neural fulcrum" may help define a target for vagal activation[45]. To encapsulate these concepts, evoked cardiac response to cervical Vagus nerve stimulation reflects an interaction between afferent and thus central stimulation and efferent activation related to the frequency, intensity, and pulse width delivered. The fulcrum is the point at which there is a null heart rate response with stimulation based on balanced afferent and efferent activation. It is, of note, that the efferent response can be blocked by muscarinic blockers but not by β-blockers, angiotensin converting enzyme inhibitors or If funny channel blockers and remains balanced.

Approaches to Electrical Autonomic Regulation

Electrical autonomic regulation includes efferent parasympathetic activation by VNS, sympathetic inhibition by SCS, and baroreflex modulation by BAT (Table 1). Regarding parasympathetic stimulation, in HFrEF, preganglionic stimulation responses are attenuated but postganglionic parasympathetic responses are preserved[46]. Theoretically, methods to enhance presynaptic parasympathetic activation may help. Local ganglionic neurotransmission may be important as some parasympathetic activation occurs via the intrinsic ANS and on local tissues[46]. However, these issues may be less important pathophysiologically than loss of parasympathetic afferent activation in HFrEF.

Vagal Nerve Stimulators

A beneficial effect of electrical parasympathetic stimulation with an efferent unidirectional right or left approach has been postulated and shown to have potential value in initial human testing and in some, but not all, animal models[37, 40, 47-56]. The first human VNS was implanted in 1988 and approved for use in focal or multifocal epilepsy [71]. Their use has since expanded to the treatment of migraines[57] and depression[58]. VNS has been utilized effectively to stimulate vagal afferents for migraine, depression, and seizure disorders[59-62]. VNS for neurological conditions are typically implanted to obtain afferent activation (Table 1). For the heart, stimulation could be efferent affecting sinus rate perhaps greater via the right rather than left Vagus. Implantation of

Table 1: Overview of Neuromodulation Device Therapies

Device	Implant Location	Target Nerve(s)	Current FDA Approved Use
Vagal Nerve Stimulator	Chest wall	Vagus nerve (cranial nerve X)	Depression, drug resistant epilepsy in patients age > 12 years old Other uses: migraines, pain control in fibromyalgia
Spinal Cord Stimulator	Epidural space, T1-T4 spinal cord level (in HF)	Dorsal nerve root, peripheral subcutaneous nerve branches	Intractable neuropathic pain Other uses: intractable angina, peripheral vascular disease
Baroreceptor Activation Therapy	Chest wall	Baroreceptors in the carotid sinus	HFrEF (≤35%) with regular heart rhythm that are not candidates for cardiac resynchronization therapy

a VNS is a surgical procedure that requires administration of general anesthesia and endotracheal intubation, usually lasting around 45-90 minutes and is not devoid of surgical risks[71].

The potential value of this therapy may depend on the cause of HF and methods of stimulation[63] including stimulation frequency, intensity, amplitude, timing (based on the QRS complex), and number of pulses per cycle. Laterality (right versus left stimulation) may make a difference. Furthermore, as the Vagus is composed of fibers with various purposes, it becomes important which fibers are stimulated. The endpoint of activation is worth considering since parasympathetic nerve activation has multiple effects not necessarily reflected in heart rate alone or even at all; the ultimate goal is to improve functionality and survival.

Spinal Cord Stimulators

SCSs are used currently as a nonpharmacological approach to treat chronic pain, notably neuropathic or ischemic pain including chronic angina. SCS devices inhibit sympathetic cardiac efferent signaling and, as such, may provide benefit in HF patients[47-50]. Implantation involves a two-stage process: a trial period to evaluate efficacy followed by permanent implantation. These stages are performed under fluoroscopic guidance in an outpatient setting, typically under local anesthesia. During implantation, the epidural space is accessed, and leads are placed at the T1-T3 level to stimulate the dorsal aspect of the spinal cord. It is postulated that SCS suppresses sympathetic activity by affecting both afferent and efferent fibers of intrinsic cardiac neurons[73].

Baroreceptor Activation Therapy

BAT was originally studied in resistant hypertension[43,69,70]. It has been investigated to treat HFrEF[46,57,58,64,65]. BAT affects autonomic regulation by stimulation near the carotid bifurcation affecting afferent activation and subsequent sympathoinhibition[64-67]. The device is implanted in the upper chest with leads placed in the neck over the carotid artery. It is hypothesized that arterial baroreflexes, including carotid sinus baroreflex, have reduced sensitivity in chronic HF. These reflexes normally inhibit sympathetic outflow. However, in chronic HF, sympathetic outflow proceeds uninhibited[68]. Stimulation generating blood pressure reduction indicates proper positioning. Sympathetic outflow is suppressed directly in addition to potential effects on afferent parasympathetic activation. Based on recent FDA approval, Baro-stim HF is now available for implantation to treat HFrEF – it is the only FDA approved autonomic device for this indication[68].

Renal Nerve Ablation

Renal nerve ablation, not a device therapy, and not a focus of this review, nevertheless, deserves mention. In high sympathetic states, such as, HF, efferent sympathetic signals cause sodium retention and reduce renal blood flow. In chronic HF, renal sympathetic efferent signals activate the renin-angiotensin-aldosterone system releasing adenosine, angiotensin II, and markers of oxidative stress to the central nervous system to feed a cycle of sympathetic overactivity. The paraventricular nucleus, the rostral ventrolateral medulla, and the area postrema appear to be responsible for release of norepinephrine, causing excess oxidative stress, and inflammation[69]. Ultimately, arterial vasoconstriction, endothelial dysfunction, cardiac remodeling, fibrosis, ischemia, and arrhythmias may follow. Renal nerve ablation, initially attempted in the 1950s for resistant hypertension, has been studied to treat HF. This endovascular procedure purportedly leads to the ablation of renal afferent and efferent sympathetic fibers.

Pre-clinical Trials – in Animal Models

Vagal Nerve Stimulation

In 1991, Vanoli[70] evaluated utilization of VNS in canines one month after the animals had a two-stage ligation of the left anterior descending coronary artery to create an anterior wall myocardial infarction. Stress tests were performed, during which, the circumflex artery was occluded to initiate ischemic ventricular fibrillation. The animals were assigned to control or vagal nerve stimulation. Stress testing and circumflex occlusion was repeated. The VNS group had heart rates 75 bpm slower than the controls (255 vs 170 bpm). Only 10% of the animals experienced repeated ventricular fibrillation with VNS vs. 92% in the control group.

In 2004, Li[71] found a 73% relative reduction in mortality at 140 days in rats with HF treated with VNS after myocardial infarction secondary to left coronary artery ligation. Fourteen days post-myocardial infarction, survivors were randomized to VNS or sham intervention. In the treatment group, VNS was titrated to decrease heart rate by 20-30 bpm and continued for 6 weeks. Besides decreasing mortality, the treatment group had significantly lower left ventricular end-diastolic pressure, lower biventricular weight and improved maximum dP/dt, a surrogate measure of contractility. VNS decreased mortality presumably by preventing cardiac remodeling. A follow-up study in the same rats[72] showed that VNS titrated to reduce heart rate by 20-30 bpm also decreased premature ventricular contractions.

Subsequent studies considered potential mechanisms of VNS benefit. Sabbah[8, 73] showed that in canines with micro-embolism-induced infarcts and with HFrEF, VNS improved left ventricular ejection fraction, prevented increases in left ventricular end-diastolic volume, decreased left ventricular end-systolic volumes, and resulted in lower inflammatory markers (TNF-alpha, IL-6) versus sham stimulation. The treatment group experienced a decrease in heart rate by 28 bpm. VNS improved ventricular function and prevented remodeling presumably by controlling heart rate and preventing inflammation.

In a rat HF model, induced by left anterior descending coronary

Table 2: Neuromodulation Device Therapies and Major Heart Failure Clinical Trials

A. Vagal Nerve Stimulation

Trial	Design	Size	Study Population	Control	Endpoints	Intervention	Outcome	Follow Up
De Ferrari (2009)	Multi-center, international	32	18-75 yo NYHA Class II-III HFrEF (LVEF ≤35%) on optimal medical treatment	None	1˚: Adverse Events 2˚: NYHA class, quality of life, 6-min walk test, LV end-diastolic & end-systolic volumes	Right vagal stimulation Delivered phasic pulses synchronous with heartbeat Efferent fibers Frequency 1-2 Hz Mean intensity 4.1±1.2 mA	Demonstrated safety of VNS Improvement in LVEF, LV end-diastolic volume, NYHA functional class, quality-of-life, 6-min walk	3, 6, 12 months
NECTAR-HF (2011)	Multi-center, randomized, sham-controlled, phase II	96	NYHA Class II-III HFrEF (LVEF ≤35%, LVED diameter >55 mm) on optimal medical treatment	Sham Procedure	1˚: LV end-systolic diameter 2˚: NYHA class, quality of life, LVEF, functional capacity, plasma biomarkers	Right vagal activation Randomized to "on" and "off" groups, 10 sec/min Frequency 20 Hz Mean intensity 1.3±0.8 mA	Demonstrated safety of VNS, improvement in quality-of-life, NYHA functional class No changes in LV end systolic diameter or echocardiographic parameters	6, 12, 18 months
ANTHEM-HF (2012-2013)	Multi-center, open-label, phase II	60	NYHA Class II-III (LVEF ≤ 40%) on optimal medical treatment	None	1˚: Adverse Events, changes in LVEF, LV end-systolic volume 2˚: NYHA class, quality of life, 6-min walk test, LV end-systolic volumes, mean HR, HR variability, plasma biomarkers	Randomized to left or right vagal stimulation Continuous cyclic stimulation Frequency 10 Hz, Pulse width 250 µs Mean intensity 2.0±0.6 mA	Demonstrated safety & efficacy of VNS Improvements in LVEF, LV end-systolic and end-diastolic volumes, NYHA class, 6-min walk test, quality of life Decreased mean heart rate, increase heart rate variability	6, 12, 42 months
INOVATE-HF (2011-2015)	Multi-center, international, randomized, controlled trial	707	≥18 yo NYHA Class III HFrEF (EF ≤40%) on optimal medical therapy	Guideline directed medical therapy	1˚: All-cause mortality, hospitalization 2˚: NYHA class, 6-min walk test, LV end-systolic volume index, quality of life	Right vagal activation Frequency 1-2 Hz Mean intensity 3.9±1.0 mA	VNS did not reduce mortality of hospitalization for heart failure	Terminated early due to futility

B. Spinal Cord Stimulation

Trial	Design	Size	Study Population	Control	Endpoints	Intervention	Outcome	Follow Up
SCS HEART (2011 – 2013)	Single blinded, randomized controlled trial	22	NYHA class III HFrEF (LVEF 20-35%), implanted defibrillator device, and LV end-diastolic diameter 55 – 80 mm on stable optimal medical therapy	None	1˚: Death due to ventricular tachyarrhythmia, sudden unexplained death, MI, or HF hospitalization in 6 months 2˚: device malfunction, incidence of ventricular tachyarrhythmia, long term safety of SCS at 24 months	24 hr/day Frequency 50 Hz, pulse width 200 µs	Demonstrated safety and feasibility of SCS Improvement in NYHA class, quality-of-life, VO2 max, LVEF, and LV end systolic volume at 6 months	6, 24 months
DEFEAT-HF (2010 – 2013)	Prospective, multi-center, parallel, single-blind, controlled trial	81	NYHA III HFrEF (LVEF ≤35%), QRS duration <120 ms, LV end-diastolic dimension 55-80 mm, on optimal medical treatment	"Off" group receiving guideline directed medical therapy	1˚: Change in LV end-systolic volume index 2˚: peak VO2, NT-pro-BNP	Randomized to "on" and "off" groups, 12 hr/day, crossover to "on" at 6 months Frequency 50 Hz, Pulse duration 2oo µs	Demonstrated safety of SCS No improvement in LV end-systolic volume index at 6 months No improvement in peak VO2 or NT-pro BNP	6, 12 months

C. Baroreceptor Activation Therapy

Trial	Design	Size	Study Population	Control	Endpoints	Intervention	Outcome	Follow Up
Gronda et al[80] (2016)	Open label, single center, proof of concept trial	18	NYHA Class III HFrEF (LVEF ≤40%), 6-minute walk distance 150-450 meters, resting heart rate 60-100 beats per minute, estimated glomerular filtration rate ≥ 40 mL/min/1.73m2	Guideline directed medical therapy	Central blood pressure, pulse wave velocity, arterial stiffness	Chronic activation (Barostim Neo device) Afferent activation	No significant change in central blood pressure, pulse wave velocity, or arterial stiffness	3 months

Abraham et al[81] (2015)	Multinational, prospective, randomized, parallel-controlled clinical trial	146	NYHA Class III (LVEF ≤ 35%), on chronic optimal medical treatment, 6-minute walk test distance 150 – 450 meters, resting heart rate 60-100 beats per minute, systolic blood pressure ≥ 100 mmHg, glomerular filtration rate ≥30 mL/min/1.73m2	Guideline directed medical therapy	1° (Safety): event-free rate of all system and procedure related adverse cardiovascular and neurological events 2° (Efficacy): changes in NYHA functional class, quality of life score, 6-minute walk test	Chronic activation (Barostim Neo device) Afferent activation	Demonstrated safety & efficacy Improvements in 6-minute walk distance, quality of life score, NYHA class	6 months
BeAT-HF Trial* (2019) *(NCT02627196)	Prospective 2-phase randomized controlled trial	408	NYHA Class III (LVEF ≤ 35%), not eligible for cardiac resynchronization therapy	Guideline directed medical therapy	1° (Efficacy): 6-minute walk test, quality of life score, NT-proBNP	Chronic activation (Barostim Neo device) Afferent activation	Improvements in 6-minute walk test, quality-of-life scores, NT-proBNP	6 months

ligation, VNS improved left ventricular ejection fraction and attenuated interstitial fibrosis versus sham stimulation[74]. In addition, with VNS, elevated plasma norepinephrine and dopamine levels improved and dysfunctional Ca+2 handling was reversed in sarcoplasmic reticulum Ca+2 ATPase, the Na+/Ca+2 exchanger 1 and phospholamban[74].

Zhou[75] performed low-level, transcutaneous stimulation of the Vagus nerve afferents via the tragus in a hypertensive rat model of HF with preserved ejection fraction. Compared to sham stimulation, low-level tragus stimulation attenuated blood pressure, prevented deterioration of diastolic function, attenuated left ventricular inflammatory cell infiltration and fibrosis and affected tumor necrosis factor, osteopontin, interleukin (IL)-11, IL-18 and IL-23[75].

Shinlapawittayatorn[76, 77] studied an ischemia reperfusion swine model and found that vagal nerve stimulation reduces infarct size, improved ventricular function, decreased ventricular fibrillation episodes, attenuated mitochondrial reactive oxygen species, affected cytochrome c release; and increased phosphorylated connexin 43 and interleukin 4a levels but these benefits depended on timing with respect to ischemia. Effects were abolished by atropine indicating the importance of muscarinic receptor activation during vagal stimulation.

Spinal Cord Stimulation

Lopshire[78] showed an improvement in ventricular systolic function, reverse remodeling, and decreased arrhythmias in a canine model of HFrEF treated using SCS. HF was induced by left anterior descending coronary artery ligation and right ventricular pacing at 240 bpm for 3 weeks. Canines were randomized to SCS, medical therapy, or control. Pacing was stopped and all animal models had some spontaneous increase in left ventricular ejection fraction. However, SCS greatly accelerated and improved left ventricular ejection fraction recovery, normalized diastolic and systolic dimensions, incurred favorable changes in brain natriuretic peptide, accelerated normalization of norepinephrine levels, and decreased arrhythmic events.

Liu[79] studied if SCS had immediate effects. They induced HF via coronary artery ligation and with rapid ventricular pacing in a porcine model. SCS for 15 minutes at 24-hours post-ischemia improved ejection fraction, increased contractility (dP/dtmax) and decreased intraventricular dyssynchrony. Despite this, myocardial oxygen consumption decreased. The beneficial effects reversed after interruption of SCS but were reproduced with repeat applications.

Baroreceptor Activation Therapy

Zucker[67] induced HFrEF in a canine model via rapid ventricular pacing to assess chronic baroreceptor activation. Despite continuous rapid right ventricular pacing, BAT significantly lowered mortality and lowered norepinephrine and angiotensin II levels vs. controls suggesting that the effects may be via neurohormonal suppression.

BAT has potential important antiarrhythmic effects over the long term. In a microembolization-induced HFrEF canine model, Wang[80, 81] attempted to induce ventricular tachycardia or fibrillation (with isoproterenol, if needed). After 6 months of BAT, only 29% of the animals were inducible whereas 100% of controls were. In addition, more aggressive stimulation was required to induce ventricular tachyarrhythmias in the BAT treated group. Thus, pre-clinical studies indicate that autonomic modulation has potential to decrease morbidity and mortality in HF patients. These studies suggest that several devices may be useful and by various mechanisms.

Clinical Trials (Table 2)

Vagal Nerve Stimulation

De Ferrari et al[82, 83] conducted a pilot study without a control group to evaluate efficacy of VNS in HF. Patients with HFrEF taking guideline-suggested medical therapy underwent VNS implantation with phasic up-titrated protocol (25% on vs 75% off) with a stimulation amplitude up to 5.5 mA, heart rate reduction of 5-10 bpm, or occurrence of side-effects. Safety and efficacy of VNS in some soft clinical endpoints were demonstrated after 3 months of stimulation. Effects were maintained at 1 year.

Neural Cardiac Therapy for Heart Failure Study (NECTAR-HF)[49, 84] was a multi-center, randomized, sham-controlled clinical trial. A similar patient group was included in the study. Patients were randomized to low-amplitude, high-frequency, open-loop, intermittent, right-sided

VNS vs. sham (VNS "off") for 6 months, followed by VNS "on" in all patients for 6-18 months. The frequency of stimulation was 20 Hz, the current intensity reaching an average of 1.3±0.8 mA and limited by side effects. Although there was a statistically significant improvement in NYHA class and quality-of-life, there was no change in hard endpoints, i.e., left ventricular end-systolic diameter or other echocardiographic parameters. The intensity of stimulation was considered a limitation as up-titration was difficult due to side effects. There were no significant changes in heart rate variability. Thus, vagal nerve activation may not have been potent enough to elicit a change. Furthermore, it may depend on the frequency and intensity and bidirectionality of vagal nerve stimulation. In the study, likely, there was some degree of bidirectional stimulation, but this could not be demonstrated with certainty.

Bio Control created a device purported to deliver unidirectional efferent VNS. The implant was right-sided and the device delivered single pulse synchronized per cardiac cycle with duty cycle of 21±5%, stimulation intensity of 5.5 mA maximum up-titration until discomfort or pain. In Increase of Vagal Tone in Heart Failure (INOVATE-HF)[50, 85] trial, the patients with NYHA class III HFrEF (EF≤40%) and left ventricular end-diastolic diameter of 50-80 mm were included in the study. The treatment group received closed-loop, intermittent, high-amplitude and low-frequency asymmetric pulsations via the right Vagus nerve, while the control group received guideline-directed medical therapy. There was no sham control. Up-titration in vagal stimulation was limited by pain. The study was terminated early due to futility as VNS did not reduce the primary endpoint, in this pivotal trial, of cardiovascular death or HF events, nor did it improve left ventricular end-systolic volume, though quality-of-life, NYHA class, and 6-minute walk distance did improve significantly. It was therefore possible that efferent stimulation was not strong enough or that afferent activation was also necessary.

In Autonomic Regulation Therapy for the improvement of Left Ventricular Function and Heart Failure Symptoms (ANTHEM) trial, right and left vagal nerve stimulation were compared in 60 NYHA class II-III HF patients[86]. Stimulation parameters were adjusted over a titration phase (pulse width of 250 μs and frequency of 10 Hz with a mean output of 2.0±0.6 mA). At six months, there were significant improvements in ejection fraction, ventricular end-diastolic diameter, heart rate variability, and Minnesota Living with Heart Failure questionnaire as well as a six-minute walk distance. Functional class improved in 77% of patients. With continued follow-up, benefits persisted[87].

Spinal Cord Stimulation

Tse[88] conducted the thoracic Spinal Cord Stimulation for HF as restorative treatment (SCS HEART) multicenter-prospective trial. It was the first pilot study evaluating safety and efficacy of SCS in HF. Of 22 patients enrolled, SCS implantation at the thoracic 1-3 level programmed chronically at frequency of 50 Hz and pulse width of 200 μs (based on results of preclinical trials) showed the safety and feasibility of SCS in HF patients. There was improvement in NYHA class, quality-of-life, VO2max, ejection fraction, and left ventricular end-systolic volume at 6 months. The study was limited by a small sample size and no control group.

In the DEFEAT-HF trial, patients were randomized to SCS "on" vs "off", with crossover to "on" at 6 months[89]. Stimulation was 12 hours/day based on individual sleep/wake cycles, 50 Hz, 200 ms pulse, at 90% of maximally tolerated voltage. At 6 and 12 months, the primary and secondary outcomes were similar between groups. No physiologic markers assessed autonomic regulation, but the study was "defeated" by being underpowered.

Baroreceptor Activation Therapy

BAT[64] was firstly tested in 383 patients with resistant hypertension, of whom, 143 completed 5 years of follow-up. Systolic blood pressure and heart rate fell from 179±24 to 144±28 mm Hg (P<0.0001) and from 74±15 to 71±13 bpm (P<0.02), respectively. These effects were higher in patients with HF. Then, the effect of BAT was studied in a HF population. In the first study, BAT was compared with optimal medical treatment[90]. At 3 months, BAT did not improve central BP but did improve muscle sympathetic nerve activity, NYHA class, Minnesota Living with Heart Failure Questionnaire score, the number of HF medications, and six-minute walk distance.

The safety and efficacy of BAT were assessed in 2 randomized-controlled trials. In the first one, patients with NYHA class III HF and ejection fractions ≤35% were randomized to guideline-directed medical therapy alone (n=70) or ongoing therapy plus BAT (n=76) for 6 months[91]. Those assigned to BAT had improvements in 6-minute walk distance (59.6±14 meters vs. 1.5±13.2 meters; p = 0.004), quality-of-life score (-17.4±2.8 points vs. 2.1±3.1 points; p < 0.001), and NYHA class (p = 0.002 for change in distribution).

The BeAT-HF (NCT02627196) was a prospective two-phase randomized controlled trial of patients taking guideline-directed medical and device therapy with or without BAT. Patients with HFrEF who are not eligible for cardiac resynchronization therapy were enrolled[92]. The first phase effectiveness endpoints were 6-month changes in 6-minute hall walk distance, Minnesota Living with Heart Failure Quality-of-Life score, and NT-proBNP. Data collection included recurrent HF hospitalizations and cardiovascular mortality. Of 408 patients, 184/199 had BAT implanted successfully. At 6 months, there was improvement in 6-minute walk test (by 60 meters), Minnesota Living with Heart Failure, Quality of Life (by 14 points), and NT-proBNP (by 24%)[93].

Renal Nerve Ablation

The Renal Artery Denervation in Chronic Heart Failure (REACH-Pilot) evaluated the safety of bilateral percutaneous renal nerve denervation for HFrEF[94] in 7 patients on maximally-tolerated guideline-directed medical therapy. No procedural complications were noted and, at 6-months, there was an insignificant trend toward blood pressure reduction. All reported symptomatic improvement in 6-minute walk test[85] but with no control group, no conclusions could be drawn.

In a single-center, prospective, controlled study, Gao[95] randomized 60 HFrEF patients to renal nerve ablation vs. drug treatment alone and, at 6 months, the renal nerve denervation group had reduction in N-terminal pro-BNP (440.1±226.5 vs. 790.8±287.0 pg/mL, p< 0.001), an increase in ejection fraction (39.1±7.3% vs. 35.6±3.3%, p=0.017) and

improved NYHA class (p = 0.01) without adverse effects.

Chen et al[96] also conducted a randomized, controlled pilot study in 60 patients with symptomatic HFrEF (EF≤40%) taking maximally tolerated guideline-directed medical therapy to assess the safety and efficacy of renal nerve ablation versus optimal medical therapy alone. No procedural complications were noted. At 6-month follow up, the ejection fraction improved in renal nerve ablation cohort (31±5.7% vs 42±7.9%, p<0.001). Patients in the renal nerve ablation group had an improvement in left ventricular ejection fraction (p <0.001), 6-minute walk test (p=0.043), NYHA class (p< 0.001), NT-proBNP (p<0.001) and presting heart rate (p=0.008). The study was limited by small sample size and no placebo intervention.

While safety of renal nerve ablation seems feasible in small trials, larger trials are needed to establish efficacy against an adequate control group in patients with HFrEF.

Why Were Clinical Trials Not Consistently Beneficial for HFrEF?

Why have pre-clinical and pilot studies been so promising, while clinical trials have not all been definitive? One striking difference between pre-clinical/pilot studies and clinical trials is that in pre-clinical and pilot studies, device therapy has been titrated to decreases in heart rate and increases in heart rate variability, known markers of vagal activation and/or sympathetic inhibition. In the clinical trials, device therapy has been started at arbitrary amplitudes and frequency values below this level expecting benefit but without confidence of or evidence for autonomic regulation. Another factor is the complexity of the ANS. With regard to VNS, the vagal activation can have multiple effects dependent on fibers activated and directionality of activation. VNS, as delivered, may or may not stimulate the fibers required to affect outcomes. Some effects of parasympathetic nerve stimulation may be anti-inflammatory but others effect heart rate or contractility. However, part of the problem may be getting the dose right and the proper fibers stimulated. Substantial differences in stimulation approaches, neural targets, fibers recruited in vagal nerve stimulation delivery, and expected responses to that stimulation must be considered in terms of outcomes of the trials[47]. Hopefully, the neural fulcrum approach will help with choosing the proper stimulation dosing. Maybe afferent fibers are being stimulated but not efferent. Should we stimulate the right Vagus, the left, or both? Should we stimulate centrally, peripherally, or both? Is amplitude more important or is frequency? Is there a specific ratio of amplitude to frequency that is most effective? Should stimulation be phasic or tonic? Would benefit be seen initially after diagnosis of HF to prevent long-term scarring and remodeling, or can it be seen in chronic HF? Much work is needed to answer these questions.

Patient selection may be critical. In animal studies, HFrEF was secondary to induced myocardial infarction or tachycardia pacing, both of which are high sympathetic, low parasympathetic tone states. The etiology of HFrEF was not taken into consideration in clinical trials.

Another issue is determining which type of autonomic intervention is most effective. Is VNS or BAT preferred? Can patients even tolerate the "dose" needed to produce the desired autonomic effects prior to unwanted side effects, as seen as a limitation in the INOVATE-HF trial? If patients cannot tolerate the stimulation needed, is this all just a theoretical benefit with futility in performing further clinical trials? More data are needed.

Should Autonomic "Normalization" be the Goal?

Regulation of the ANS has focused on stimulating the parasympathetic nervous system and inhibiting the sympathetic nervous system. However, "normalization" of the ANS should be sought assuming that the "dysregulation" seen is actually maladaptive. What is the perfect balance?

Where Are We Now?

The pre-clinical and pilot data are intriguing but results from clinical trials to date are puzzling and inconclusive. Other clinical trials are currently underway. The ANTHEM-HF pilot study (and an extended version)[86, 97] randomized patients with NYHA Class II-III HFrEF (left ventricular ejection fraction <40%, left ventricular end-diastolic diameter 50-80 mm) to left- or right-sided VNS with no control group. VNS was titrated based on heart rate dynamics (decrease in mean heart rate, heart rate variability). Safety endpoints were met, and, at 12 and 42 months, there were significant improvements in left ventricular ejection fraction, left ventricular end systolic and diastolic volumes, NYHA class, 6-minute walk distance, and quality-of-life. Additionally, decreased mean heart rate and increased heart rate variability were noted.

While the pilot study was promising, mortality was not evaluated, and there was no control group. Thus, the ANTHEM-HFrEF randomized, controlled, clinical trial is currently underway, using the same intervention. Inclusion criteria include patients with NYHA class II-III HFrEF (ejection fraction ≤35%, left ventricular end-diastolic diameter <80 mm) on stable guideline directed medical therapy with NT-proBNP >800 pg/mL and 6-minute walk distance 150-450 meters, limited by HF symptoms. The primary endpoint is a composite of reduction of cardiovascular death and HF hospitalizations. Secondary outcomes include symptom reduction and physical functioning.

Several renal nerve ablation studies are underway, including RELIEVE and SYMPLICITY-HF. Due to the immense potential of, and interest in, autonomic regulation, more studies are on the horizon. An ESC(European Society of Cardiology) scientific position statement[98] has been written on the topic of the ANS as a therapeutic target in HF but, since then, there have been advances and we expect there will continue to be.

Conclusions

HFrEF commonly co-exists with excess sympathetic tone and impaired parasympathetic tone at rest and with exercise. Consequences can be devastating. Autonomic regulation has the potential to correct the imbalance and improve outcomes. While pre-clinical trials and pilot studies are promising, clinical trials have not shown definitive reduction in mortality or objective secondary endpoints. Some studies have shown benefit, however, but it is clear that the type of stimulation is critical. Despite substantial limitations of many of the studies reported so far, much has been learned. Autonomic modulation is complex to regulate. Trials are underway building on the knowledge gained from prior data.

HFrEF remains a major problem without easy solutions. Autonomic modulation holds promises as a major breakthrough to treat our severely disabled patients with HFrEF.

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