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Autonomic Regulation Therapy in Heart Failure

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Abstract

Autonomic Regulation Therapy (ART) is a rapidly emerging therapy in the management of congestive heart failure secondary to systolic dysfunction. Modulation of the cardiac neuronal hierarchy can be achieved with bioelectronics modulation of the spinal cord, cervical vagus, baroreceptor, or renal nerve ablation. This review will discuss relevant preclinical and clinical research in ART for systolic heart failure. Understanding mechanistically what is being stimulated within the autonomic nervous system by such device-based therapy and how the system reacts to such stimuli is essential for optimizing stimulation parameters and for the future development of effective ART.

Keywords

Heart failure; sympathetic modulation; vagus nerve stimulation; spinal cord stimulation; baroreceptor stimulation; renal denervation

Introduction

In the United States, 1 in 9 deaths each year is related to heart failure with an estimated 5.1 million people affected [1]. The cost of heart failure is thought to be about 32 billion dollars per year as a result of costs to the health service, medications, and absenteeism in the work force [2]. Heart failure continues to have a high mortality rate, despite advances in pharmacological and device therapy, with the Framingham study reporting a median 5 year

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Compliance with Ethics Guidelines

Conflict of Interest: Jeffrey L. Ardell serves as a scientific advisor to Cyberonics, Inc Kalyanam Shivkumar and Una Buckley declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of UCLA, the National Institutes of Health and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards]. All procedures performed in studies involving animals were in accordance with the ethical standards of East Tennessee State University and University of California Los Angeles.

survival of 25% in men and 38% in women [3]. Early diagnosis and treatment may impact the morbidity and mortality [4]. Given the aging population, increase in obesity, diabetes mellitus, and sedentary lifestyle, it is thought that these statistics largely underestimate the prevalence [5-7]. While these statistics include all forms of heart failure, this review will specifically focus on autonomic modulating device therapy in the setting of heart failure with reduced ejection fraction.

Structure/function organization of the cardiac neuronal hierarchy

Cardiac control is achieved through a hierarchal network that may be considered in three-levels [8-10]. *Level 1: CNS neurons* (medullary and spinal cord neurons modulated by higher centers); *Level 2: Peripheral*: extracardiac-intrathoracic neuronal pool; and *Level 3: Peripheral:* the intrinsic cardiac nervous (ICN) system (Figure 1).

The peripheral layers (Levels 2 and 3) form cardio-centric loops, while the CNS (Level 1) engages neural mechanisms for cardiac and peripheral vasculature regulation [9, 10]. Acting together, these hierarchical populations coordinate and regulate regional cardiac electrical and mechanical indices throughout each cardiac cycle to assure that cardiac output matches blood flow demands [11-13]. To understand network interactions within and between levels 1-3, one must first understand the characteristics of its constituent parts. It is through such understanding that rational neuromodulation therapies can be devised.

Afferent neurons—Afferent neurons associated with cardiac and major vascular sensory neurites transduce the local mechanical and/or chemical milieu of these tissues [14]. The somata of these cardiac and vascular sensory neurons are located in: i) nodose ganglia; ii) dorsal root ganglia; iii) intrathoracic extracardiac ganglia; and iv) intrinsic cardiac ganglia [14]. The majority of these somata transduce mechanical distortion, the chemical milieu or both to second order neurons in the CNS and periphery [14-16]. Cardiac sensory information is fed into each of the three ‘levels’ of the neuronal hierarchy, these sensory inputs are a primary initiator of responses within and between the different levels of the neuraxis [10, 17, 18].

Efferent neurons—Efferent neuronal outflow from the autonomic nervous system to the heart depends on central and peripheral mediated neural reflexes [10, 19, 20]. Cardiac-related parasympathetic efferent preganglionic somata are localized at medullary sites (primarily the Nucleus Ambiguus [NA]) and project to post-ganglionic neurons within intrinsic cardiac ganglia [21-24]. Sympathetic preganglionic efferents for cardiac control are localized at the intermedio-lateral cell column of the spinal cord (T1-T5) [24]. They project to postganglionic neurons located in stellate, middle cervical, superior cervical, mediastinal and intrinsic cardiac ganglia [24, 25]. Within each nexus point of the neuronal hierarchy for cardiac control, from the CNS to intrinsic cardiac ganglia, network interactions within and between levels is fundamental to network output function (Fig. 1).

Local circuit neurons (LCN)—LCNs are neurons that are not directly transducing cardiac indices (cardiac afferent neurons) or having direct motor function, but clearly play a role to integrate sensory inputs along with inputs from the central nervous system. These

neurons are located throughout all intrathoracic ganglia, including those distributed on the heart [10, 12, 26]. They receive sensory feedback from the heart and intrathoracic veins and arteries that is multi-dimensional since most sensory neurons transduce both the regional mechanical and the chemical milieus [12, 27, 28]. Their activity is likewise altered by autonomic neural inputs [12]. This population of neurons represents the dominant sub-class of neurons contained within the intrinsic cardiac nervous system and sub-serves major neuronal processing within that network [10].

Autonomic dysregulation is central to the evolution of cardiac pathology [17, 18, 29]. Mechanistically, this reflects reactive and adaptive responses of the cardiac neural hierarchy that derive from sensory transduction of the stressed/diseased myocardium [17, 30, 31]. Such changes in neural processing manifest themselves throughout the neuraxis including at the intrinsic cardiac nervous system, intra-thoracic sympathetic ganglia, spinal cord, brainstem and multiple central regions up to the insular cortex [10, 15, 19, 32]. This functional reorganization leads to a conflict between central and peripheral aspects of the hierarchy [18, 30, 33]. Altered neural processing leads to maladaptive responses that ultimately results in excessive sympathetic overdrive; [18, 31, 34, 35] that in turn contributes to the development of cardiac disease including fatal arrhythmias and heart failure [17, 29]. It is through the understanding of such hierarchical control and how it adapts that a rationale mechanistic based approach can be devised to effectively target specific neural processing of the cardiac nervous system to therapeutically manage cardiac pathology. Figure 1 illustrates several of these neural nexus points and serves as the focal point around which device based neuromodulation actions/reactions must be considered.

Vagal Nerve Stimulation (VNS)

When considering effects of any bio-electronic approach for neuromodulation one must consider both direct and reactive responses. The vagus can be stimulated in many different ways, at a number of different levels, and for multiple pathologies [36-38]. In each case, one must consider the characteristics of the nerves being stimulated (afferent/efferent) and the potential impact of stimulation parameters (frequency, intensity, pulse width, waveform and duty cycle). Ultimately these factors impact both off-target adverse effects and more importantly the efficacy of the applied therapy. With respect to VNS, emerging technologies for cardiovascular disease involve either direct implant of electrodes onto the cervical vagus or non-invasive stimulation via the auricular branch of the cervical vagus. This is an emerging area and our understanding of vagal nerve stimulation is still rudimentary.

VNS preclinical results

In preclinical studies, VNS has documented efficacy to impact cardiac electrical and mechanical function. In a rabbit model, VNS damped the cardiac electrophysiological restitution curve with a corresponding reduction in potential for ventricular fibrillation [39, 40]. In a porcine model, VNS applied against the stress imposed by acute ischemia-reperfusion was effective in reducing infarct size, stabilizing cardiac electrical function and in protecting mitochondrial function [41]. In an acute canine model, the effects of VNS were evaluated against an elevated sympathetic background as induced by left stellate ganglion (LSG) stimulation [42]. They demonstrated that LSG stimulation resulted in increased ventricular

instability and change in spatial heterogeneity which was reversed with VNS. They also showed that LSG stimulation with VNS resulted in a higher VF threshold compared to LSG alone. Vanoli et al [43] likewise demonstrated the efficacy of vagal stimulation to prevent sudden death in a canine model with healed myocardial infarction. Since heart failure is associated with a higher risk for sudden cardiac death, neuromodulation therapies that stabilize cardiac electrical function are of obvious clinical importance.

Pre-clinical studies have demonstrated efficacy for VNS to impact the progression of heart failure. In the rat infarct model with heart failure, VNS improved hemodynamics, left ventricular remodelling, and reduced neurohormonal activation [44]. This study demonstrated a reduction in mortality rate at 140 days from 50% in the sham model to 14% with VNS stimulation [44]. In this rat study, VNS was applied at 20Hz, 16% duty cycle (10 sec on, 50 sec off) and at an intensity that decreased the heart rate by 20-30 beats per minute. In the canine pacing induced heart failure model, VNS was associated with an improvement in left ventricular dimensions and down-regulation of important heart failure-related biomarkers including norepinephrine, angiotensin II, and C-reactive protein [45]. In that study VN was stimulated at 20 Hz, with a 53% duty cycle (14 sec on, 12 sec off) and with an intensity sufficient to produce a ~20 beat/min decrease in heart rate. Importantly, more recent preclinical studies have demonstrated that therapeutic benefits of VNS against heart failure progression can be achieved at levels of VNS that induce minimal changes in heart rate. This includes the guinea pig pressure overload model [46] with right cervical vagal stimulation (20 Hz, 22% duty cycle [14 sec on, 48 sec off]) and with bilateral non-invasive stimulation of the auricular branch of the vagus nerve (20Hz, 50% duty cycle [5 sec on, 5 sec off]) [47, 48]. In both studies contractile function improved and adverse indices of neurohumoral activation reduced towards control.

VNS impacts multiple levels of the hierarchy for cardiac control. Activation of descending efferent projections can mitigate sympatho-excitation via neural interactions within the intrinsic cardiac nervous system [49, 50], modulate cardio-cardiac reflexes [12] and impart cardioprotection via effects on cardiomyocytes [41]. Activation of ascending afferents can impact central reflexes including those that involve sympathetic and parasympathetic efferent outflows to the heart [19, 20, 22, 36]. Future pre-clinical studies should expand upon these concepts and consider additional factors including: 1) the impact of optimum medical therapy on neuromodulation; 2) intermittent versus continuous methodologies; 3) differential effects mediated from sites of VNS activation (e.g. intra-thoracic, cervical or auricular); and 4) efficacy against different cardiac pathologies including HFpEF (heart failure with preserved ejection fraction) and HFrEF (heart failure with reduced ejection fraction).

VNS clinical results

The ultimate endgame for preclinical studies in neuromodulation is transitioning to the clinical setting. While VNS has a long history in the treatment of epilepsy and depression [36, 51, 52] its clinical application for cardiac disease commenced in 2008. In patients with NYHA class II-III heart failure and left ventricular ejection fraction <35%, stimulation titration on the right cervical vagus commenced at 1-2Hz, synchronized to the

cardiac cycle, and with a target heart rate reduction of 5-10 beats per minute [53]. Patients were followed for 6 months. Results from this initial study included improved left ventricular systolic volume, NYHA classification and quality of life [53]. This was followed by an open-label phase II trial in patients with reduced ejection fraction and NYHA class II-IV [54]. At 6 months there was an improvement in left ventricular ejection fraction, volumes and 6 minute walk test which was maintained at one year [54]. INOVATE-HF is a continuation of this approach, with a target of 650 patients and an expected primary completion date of December 2016.

NECTAR-HF (Neural cardiac TherApy foR Heart Failure) was a randomized controlled trial with VNS in patients with ejection fraction <35%, increased LV end diastolic dimensions (>55mm), NYHA class III-IV, excluding patients with CRT devices, or QRS>130ms [55]. All patients had a VNS device implanted (Precision ™, Boston Scientific Corporation, St Paul, MN, USA) and were randomized in a 2:1 fashion to VNS on or off for 6 months. The stimulation parameters used were 20Hz with a 12.5% duty cycle (10 sec on, 50 sec off) with an average intensity of 1.42±0.8mA. This study failed to reach its primary end point of improvement in left ventricular systolic dimensions and secondary end points of improvement in other echocardiographic parameters, and circulating biomarkers. The study, however, did show an improvement in quality of life and NYHA classification. It is likely that the stimulation parameters, especially intensity, used in this trial may have contributed to the lack of efficacy.

ANTHEM-HF (Autonomic Neural regulation Therapy to Enhance Myocardial function in Heart Failure; Cyberonics, Houston, TX, USA) investigated VNS of the right or left cervical vagus in 60 patients [56]. The main inclusion criteria was ejection fraction less than 40%, LV end diastolic dimensions 50-80mm, and QRS <150ms. Patients were followed up over a 6 month period with up titrations of VNS over 10 weeks to an average intensity of 2.0 ± 0.6mA at 10Hz stimulation, and with a duty cycle of 17.5% (14 sec on, 66 sec off). There was an improvement in left ventricular ejection fraction by 4.5% but the left ventricular end systolic volume did not decrease significantly. There was again an improvement in quality of life, exercise capacity, and NYHA classification. There was no significant difference between left or right cervical vagus stimulation.

In summary, VNS has proven to be safe and feasible for use in humans in the setting of HFrEF. Future studies on VNS should focus on optimization of parameters of stimulation, patient selection and its transition where indicated into standard of care.

Spinal Cord Stimulation

Spinal Cord stimulation (SCS) has a clinical history of 20 years for the treatment of chronic pain and refractory angina pectoris [57-59]. While initially put forward based upon the gate control theory of pain [60], subsequent work has demonstrated that SCS is not a masking phenomenon, but instead fundamentally alters the neural-end organ interface. It is usually implemented by placement of a multi-pole electrode over the dorsal column of the thoracic cord and stimulation at parameter sets of 50 Hz, 200 μs pulse width, and intensities of 90% motor threshold [59, 61]. Early clinical studies speculated that the anti-anginal effects were a reflection of changes in supply/demand at the heart; however, subsequent preclinical studies

determined that SCS doesn't modulate/alter coronary blood flow or LV dynamics during ischemic stress [62], at least in the acute setting. Beyond its anti-anginal effects [61], SCS exerts multi-factorial cardio-protective influences including reducing atrial and ventricular arrhythmias [63-65], and the apoptotic potential [66, 67], while helping to preserve contractile function [11, 65]. In the acute setting its efficacy is optimum when applied pre-emptively [67], but reactive and chronic SCS therapy is also cardioprotective [63, 65].

SCS pre-clinical results

Cardiac sympathetic afferents transduce information responding to mechanical and chemical stimuli via the intrathoracic (T1-6) and cervical (C8-9) paravertebral sympathetic ganglia to the dorsal root ganglia and subsequently to the spinal cord and higher centers [14, 15, 19]. The cell bodies that convey the sympathetic afferent visceral input to the brain stem are found in lamina I, V, VII, and X in the C8-T9 dorsal horn [14, 15, 19]. Central and peripheral reflex processing of that afferent signal likewise contributes to the underlying sympatho-excitation of cardiac disease and the progression into heart failure [17, 18, 29]. As demonstrated in Figure 1, the spinal cord is one primary nexus point from which such processes can potentially be regulated with appropriate bioelectric medicine.

SCS impacts autonomic reflexes at multiple levels of the cardiac nervous system to impact basal cardiac function and its response to imposed stress. At the spinal cord itself, SCS induces the release of neuromodulators such as dynorphin, blunts the release of primary afferent related neurotransmitters such as substance P, and alters activity with sympathetic preganglionic neurons contained within the intermediolateral cell column [68, 69]. As such it thereby alters ascending signals to higher centers [15, 57, 58] and alters autonomic efferent outflows to peripheral aspects of the cardiac nervous system. Within extracardiac sympathetic ganglia the reflex sympatho-excitation imposed by transient myocardial ischemia is blunted while its basal function remains unaltered [11]. Within the intrinsic cardiac nervous system, a similar blunting of reflex responses to transient ischemic stress is also present, but its basal activity is reduce by SCS [70]; an effect that is manifest over time [71]. Subsequent studies have identified local circuit neurons as a primary target for SCS mediated therapy [64] and that SCS modifies synaptic function without directly targeting transmembrane properties of individual IC neuronal somata [63]. Overall, such influences can be best characterized as reflex stabilization across the neuraxis for cardiac control.

SCS modulation/stabilization of autonomic responsiveness is reflected in cardioprotection. SCS reduced aberrant electrophysiological activity within the myocardium in chronic animal models with reduced coronary reserve [72]. SCS in a heart failure canine model was effective at reducing ventricular arrhythmias [73], improving left ventricular contractile function, and reducing heart failure[65]. A porcine model of ischemic heart failure showed similar results with improved left ventricular function and myocardial strain with SCS [74]. Together, these studies have demonstrated safety and efficacy for SCS for treatment of cardiac pathology.

SCS clinical results

The Defeat-HF trial (NCT01112579), was a randomized, multicenter single blind study of 66 patients with systolic heart failure. The investigators used a single lead in the T2-T4

epidural region with patients randomized 3:2 ratio of stimulation ‘on’ or ‘off’, with the spinal cord stimulation for 12 hours per day. After 6 months the controls crossed over to therapy. The inclusion criteria were left ventricular ejection fraction ≤ 35%, NYHA class III, QRS duration less than 120ms, left ventricular end diastolic dimensions of 55mm to 80mm on stable heart failure treatments. The preliminary results failed to show an improvement in left ventricular function and dimensions but the device was found to be safe and SCS feasible to do [75]. There was no difference in freedom from heart failure or hospitalization between the two groups. The lack of efficacy of this trial, compared to preclinical experience, was likely due to sub-optimum stimulus paradigms, especially leaving patients untreated for 12hr/day.

The Spinal Cord Stimulation Heart study was a multicenter, prospective, pilot trial involving SCS in patients with systolic heart failure [76]. Inclusion criteria were patients with left ventricular ejection fractions around 20-30%, and NHYA class III. Eligible patients had spinal cord stimulators implanted in the T1-T3 epidural space. The stimulation parameters were 50Hz for 24 hours a day. Of the 15 patients that completed the 24 month follow up, there was an improvement in NYHA classification, quality of life, left ventricular end systolic volume and peak oxygen consumption. The study was also found to be safe in the setting of severe systolic heart failure.

In summary, preclinical and clinical studies both substantiate the safety of SCS for management of both cardiac arrhythmias and progression of heart failure. Future studies on SCS should focus on optimization of parameters of stimulation and patient selection. Additional mechanistic studies are likewise required to delineate the precise mechanisms by which SCS exerts its effects on central and peripheral aspects of the cardiac nervous system. Further studies are also required to determine what intracellular pathways are engaged by SCS to render cardiomyocytes stress resistant to ischemic and non-ischemic cardiac stressors.

Baroreceptor Stimulation

The baroreflex is a negative feedback system that is a primary controller of arterial blood pressure. Its afferent input signal derives from mechanoreceptors located in the carotid sinus and aortic arch. Indices of blood pressure are sensed by changes in vessel stretch as transduced by the sensory neurites enveloping both regions. Soma for the aortic arch mechanoreceptors are localized within the nodose ganglion while soma for the carotid sinus afferents are localized to the petrosal ganglia [14]. These signals are transmitted to the Nucleus Tractus Solitarius from which secondary projections arise for control of sympathetic and parasympathetic outflows [19]. Baroreceptor sensitivity is depressed in heart failure due to persistent enhancement of the sympathetic activity, possibly related to central angiotensin II levels [18, 77]. Impairment in baroreceptor sensitivity in heart failure is associated with increased mortality [30, 78, 79]. Baroreceptor neurons are adaptive and in the presence of persistent neurohormonal and cardiovascular responses the baroreceptors incompletely reset leading to long term alterations in sympathetic activity and arterial pressure [18, 80].

Avoidance of activation of the carotid body chemoreceptors with baroreceptor stimulation is imperative given their role in progression of heart failure by contributing to respiratory

instability and oscillatory breathing (changes in tidal volume and respiratory frequency) [81]. This can further exacerbate tonic and chemo-reflex evoked activation of the sympathetic nervous system by causing changes in pH, circulatory delay, and a decrease in systemic oxygen transport [81].

Baroreceptors can be stimulated at different points but clinically the easiest point of stimulation is at the level of the carotid sinus. While early studies with carotid sinus implants were associated with structural damage to implanted areas [82], recent advances in biotechnology have overcome such problems. Current devices are implanted with electrodes positioned in the carotid perivascular space around the sinus of the carotid arteries with a lead to a pulse generator positioned in the infraclavicular region [83, 84]. They are usually placed bilaterally. The premise for such therapy is that stimulation of the peripheral baroreceptors fibers increase afferent activity transduced to the Nucleus Tractus Solitarius, which is interpreted as an increase in blood pressure. In reflex response to that afferent signal efferent outflows (sympathetic down and parasympathetic up) are modified leading to reduction in blood pressure and heart rate.

Baroreceptor stimulation preclinical results

Preclinical studies support proof of concept for utilizing bioelectric approaches as applied to the carotid sinus to treat cardiac disease. Such stimulation was correlated with lower plasma norepinephrine, angiotensin II levels, and reduced mortality in a heart failure induced canine model [84]. Improvements in left ventricular function have been demonstrated in a canine heart failure infarct model with advanced heart failure at 3-months. Bilateral activation of the carotid sinus nerves improved left ventricle systolic and diastolic function and reduced heart rate compared to no-treatment controls [83]. Adverse structural remodelling was likewise mitigated in the treated group. No major safety issues were identified in preclinical studies utilizing carotid sinus stimulation and these studies laid the preclinical foundation for ongoing clinical trials.

Baroreceptor stimulation clinical results

Clinical trials have been taking place to determine the outcomes of the use of baroreceptor stimulation therapy in both systolic and diastolic heart failure. The use of implantable carotid sinus stimulator device (Rheos System) was initially used in hypertension (DEBuT-HT trial – Device Based Therapy in Hypertension Trial) showed a sustained blood pressure drop up to 4 years out and improvement in cardiac function [85, 86]. To corroborate this data, the Rheos Pivotal Trial, a double-blind randomized placebo-controlled trial, showed 88% maintenance in blood pressure reduction response at a 12 month period [87]. A recent study looking at baroreflex activation therapy in advanced systolic heart failure, in the setting of a narrow QRS, randomized patients to BAT or standard medical therapy. They showed an improvement in quality of life scores, NYHA classification, and NT-pro-BNP but did not show any change in left ventricular function with therapy [88].

In summary, utilization of the carotid sinus nerve stimulation to modulate baroreflex control mechanisms has proof-of-concept as a safe therapy for heart disease, but with limited experience in the clinical realm. It is likely that treatment efficacy is critically dependent on

underling pathology, so patient selection is critical. Future studies should focus on electrode interfaces, stimulus paradigms, and the potential for closed-loop feedback.

Renal axonal modulation and heart failure

The role of modulation of afferent renal sympathetic neurons has been investigated in preclinical and clinical studies in the setting of heart failure. Renal modulation was accomplished by catheter ablation of the renal arteries under fluoroscopic and/or electroanatomic mapping guidance, after confirmation of the absence of any baseline renal artery stenosis. Renal sympathetic modulation in a rat model with compensated high output heart failure secondary to atrio-venous fistula formation resulted in attenuated sodium excretion after sodium loading [89]. In post myocardial infarction rats, renal sympathetic modulation resulted in increased sodium excretion and decreased LV filling pressure with improved left ventricular function [90]. In a rabbit pacing induced heart failure model, renal sympathetic modulation modified angiotensin II release, and preserved renal flow and reno-vascular resistance [91]. In a canine model, renal sympathetic modulation in the setting of a pacing induced heart failure model reduced circulating angiotensin II, aldosterone, BNP, endothellin-1, and renalase [92]. Similarly, another canine high rate pacing induced heart failure model demonstrated reduced ventricular substrate remodelling and circulating angiotensin II and TGF-β with renal sympathetic modulation compared to controls [93]. They subsequently demonstrated that renal sympathetic modulation resulted in attenuation of substrate and electrical remodelling with less inducibility of ventricular fibrillation [94].

Renal axonal modulation clinical results

Small case series have demonstrated a reduction of arrhythmia post renal nerve denervation [95, 96]. Although this benefit is for arrhythmia burden reduction and not specifically to provide an improvement in left ventricular function there is a significant overlap. In other words, frequent lethal ventricular arrhythmias occur in the setting of LV dysfunction and congestive cardiomyopathy could result in deterioration in heart failure status.

The outcomes of multiple ongoing trials in relation to renal denervation actually directly benefiting left ventricular function will be very interesting. There is evidence to suggest benefits in preserved ejection fraction, probably as a result of an anti-hypertensive effect resulting in less structural remodelling [97]. This may not translate to a reduced ejection fraction heart failure model given that the majority of these patients have normal or reduced systolic blood pressure.

The REACH- Pilot study [98] was a feasibility study in 7 patients with NYHA class III-IV already on maximum medical therapy. These patients had heart failure with left ventricular ejection fractions (EF) of 43±15%. This study failed to show an improvement in left ventricular function but there was a reported improvement in symptoms. The REACH-Trial (NCT01639378) is an ongoing prospective, double blind, randomized control trial looking at safety and efficacy of renal sympathetic modulation in chronic heart failure. Another ongoing feasibility study is Symplicity-HF (NCT01392196) which aims to recruit about 40 NYHA class II-III patients, with EF<40%, impaired renal function and the primary end

point is safety. A smaller trial from the Czech Republic (NCT01870310) is a randomized, controlled trial in chronic heart failure with EF<35%, with primary end points of NT-proBNP levels, and secondary endpoints of hospitalization, and death due to cardiovascular causes.

Other novel methods of ANS modulation

Initiation and progression of cardiac disease is at its foundation critically dependent upon changes in afferent signalling. Modulation of such afferent signalling is an emerging target for autonomic regulation therapy. In a preclinical study, Wang et al. [35], demonstrated that they can mitigate the cardiac afferent mediated sympatho-exciatory reflex by administering Resinferatoxin (RTX) to the epicardium of an ischemic heart failure rat model. RTX works by blocking the transient receptor potential vallinoid 1 receptor and appears to reduce the cardiac afferent response. They demonstrated in comparison to sham model that RTX prevented increased left ventricular diastolic pressures, lung edema, cardiac hypertrophy, and partially reduced left ventricular dimensions in the failing heart. They also showed that by removing the afferent input there was attenuation in cardiac fibrosis, apoptosis, and reduced expression of fibrotic markers such as TGF-β in the RTX treated group.

Conclusion

Modulation of the autonomic nervous system is an emerging therapy to treat heart failure. It is predicated on using targeted bioelectric approaches to mitigate the maladaptive and excessive neurohumoral response to cardiac disease that are endogenously engaged to help maintain adequate cardiac output. These neurohumoral imbalances result in structural and functional changes within the various elements of the cardiac nervous system and in the cardiac tissues they innervate. Stabilization of imbalances within select elements of the cardiac neuronal hierarchy can reduce arrhythmogenesis and maintain myocardial viability in the setting of ischemic and non-ischemic heart disease. What is essential for this field to move forward is a mechanistic understanding of the induced changes in the neural hierarchy/cardiac interface in pathological conditions and from that knowledge to design and implement the optimum interfaces and stimulation paradigms to mitigate such adverse responses.

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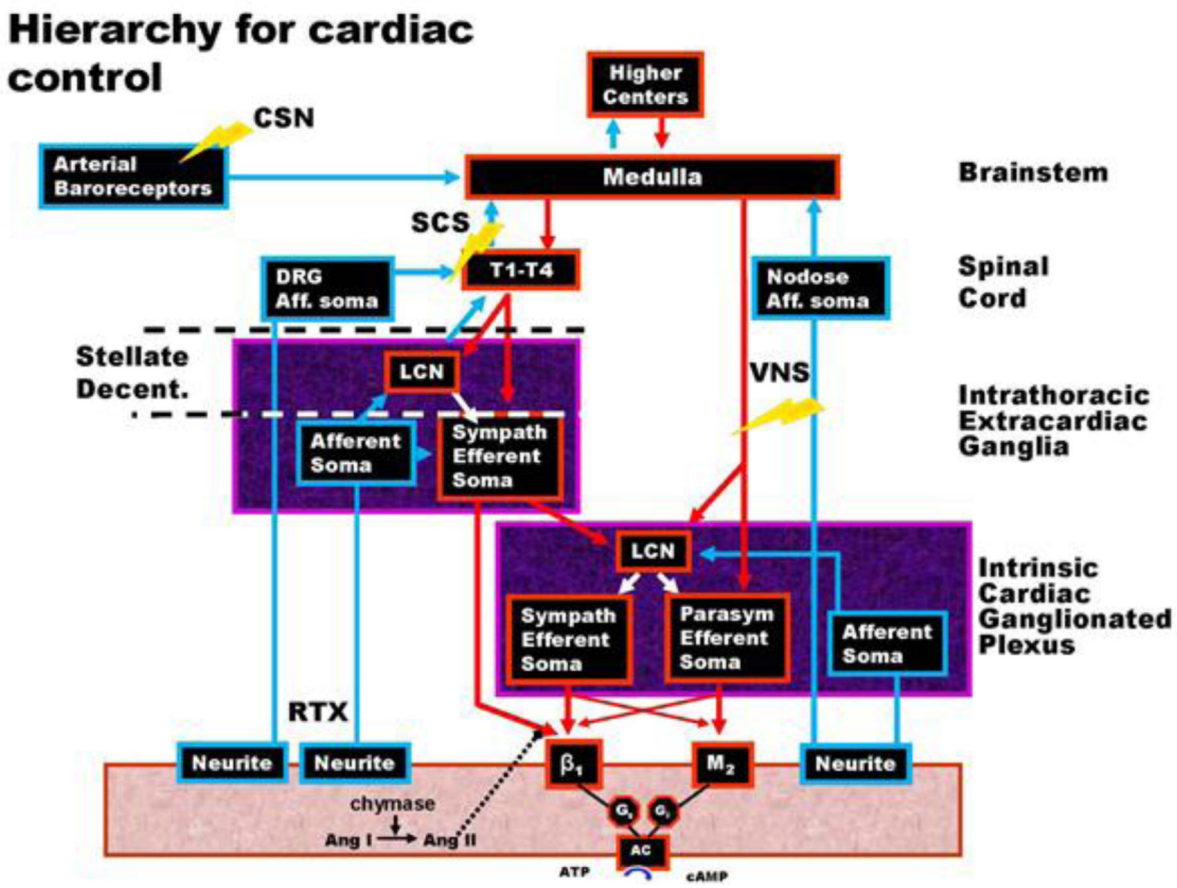

Figure 1.

This figure demonstrates the complexity of the neuronal hierarchy for cardiac control. Autonomic regulation therapy (ART) can target different structures in the cardiac neuronal hierarchy with promising results utilizing carotid sinus (CSN), dorsal column spinal cord (SCS), and cervical vagus electrical stimulation (VNS). Autonomic control can likewise be impacted by interrupting aberrant cardiac afferent signalling with Resinferatoxin (RTX) or by renal denervation. Sympath: sympathetic; Parasym: parasympathetic; LCN: local circuit neuron; DRG: Dorsal root ganglia; Aff. – afferent; T1-T4: first to 4th level of thoracic cord; Ang: Angiotensin; β: beta adrenergic receptor; M: muscarinic receptor; Gs and Gi: g proteins ; AC: adenylate cyclase; ATP: adenosine triphosphate; cAMP: cyclic-adenosine monophosphate; Neurite: sensory endings embedded in myocardium; decent: decentralization.