Atrial ganglionated plexi stimulation may be an effective therapeutic tool for the treatment of heart failure

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ABSTRACT

An autonomic imbalance, i.e., increased sympathetic tone and/or decreased parasympathetic tone is a critical characteristic of heart failure, which is associated with progressive ventricular remodeling, ventricular arrhythmia generation and disease progression. Increasing cardiac parasympathetic tone by vagus nerve stimulation has been shown to significantly improve heart failure symptoms, hemodynamics, left ventricular function and quality of life. However, cervical surgery is needed to position vagal stimulation electrode and vagus nerve stimulation may also cause some undesired side effects. Our recent studies showed that ablation of the main atrial ganglionated plexi (GP) facilitated the occurrence of ventricular arrhythmias in acute myocardial ischemic heart while low-intensity atrial GP stimulation inhibited the occurrence of ventricular arrhythmias during acute myocardial ischemia and ischemia reperfusion. Based on these results, we hypothesize that atrial GP stimulation may ameliorate autonomic dysfunction in heart failure, inhibit heart failure progression and improve heart failure prognosis.

Introduction

Heart failure is a chronic cardiovascular condition that serves as a major cause of death [1]. Heart failure has now been a major health problem all over the world due to its high prevalence, morbidity, mortality and significant health-care costs [1–3]. It has been shown in the past decades that neurohumoral activation plays an important role in the pathophysiology of heart failure. The autonomic sympathetic/parasympathetic imbalance, i.e. the activation of sympathetic nervous system and the reduction of parasympathetic activity, constitutes a fundamental element of chronic heart failure pathophysiology [4–7]. It has been shown that the autonomic imbalance is associated with progressive ventricular remodeling, ventricular arrhythmia generation and disease progression [8]. Sympathetic activation will activate renin-angiotensin-aldosterone axis and facilitate the release of other neurohormones, resulting in the increase of cardiac preload and afterload, the accumulation of plasma norepinephrine, and progressive retention of sodium and water [8]. Excessive sympathetic activation may also cause myocardial hypertrophy, apoptosis and necrosis [8]. During the time course of heart failure, down-regulation of β receptors will further attenuate the reflexes of myocardium to norepinephrine, deteriorating heart failure. In addition, parasympathetic activity reduction also occurs during heart failure pathophysiology, presenting as the weakness of vagus nerve conduction, the changes of M receptor density and constitute and the decrease of acetylcholinesterase activity [9–11]. This attenuates parasympathetic control of the heart. The combination of sympathetic activation and parasympathetic withdrawal further worsens cardiac autonomic imbalance, promoting heart failure progression.

In the light of neural mechanisms of heart failure pathophysiology, interventions, for the one hand, can be focused on the inhibition of sympathetic activation such as the application of β blockers and for the other hand, can be focused on the increase of parasympathetic activity such as using vagus nerve stimulation. Experimental studies [12–14] on heart failure have shown that vagus nerve stimulation can increase cardiac parasympathetic activity, improve hemodynamics and left ventricular function, decrease mortality and increase long-term survival rate. Two recent clinical studies [15,16] also indicated that vagus nerve stimulation could alleviate the symptoms and improve the quality of life and the left ventricular systolic function in patients with heart failure.

Hypothesis

We postulate that atrial ganglionated plexi (GP) stimulation will also improve cardiac function and prognosis outcome in heart failure.
Rationale

Functional anatomy of the atrial GP

Atrial GP are concentrated within epicardial fat pads and serve as the most important component of the intrinsic cardiac autonomic nervous system. Atrial GP are mainly located on the superior surface of the right atrium, the posterior surface of the left atrium, the posterior surface of the right atrium, the posterior medial surface of the left atrium and the inferior and lateral aspect of the posterior left atrium [17]. Atrial GP have a complex neurochemical anatomy, which include the presence of parasympathetic postganglionic neurons for its majoritv, the presence of sympathetic neurons in a subpopulation, and the innervation by a host of neurochemically non-cholinergic inputs [18].

Recent studies showed that atrial GP not only serve as relay stations that transmit central parasympathetic impulses to the heart but also function as the “integration centers” of the extrinsic and intrinsic cardiac autonomic nervous system to modulate sinus rate, atrioventricular conduction, atrial electrophysiological properties and atrial fibrillation inducibility [19–22]. Furthermore, our recent study demonstrated that atrial GP constituted a complex and integral neural network that modulated ventricular electrophysiology [23]. The ablation of the main atrial GP facilitated the occurrence of ventricular arrhythmias in acute myocardial ischemia heart [24]. On the contrary, low-intensity atrial GP stimulation significantly inhibited the incidence of ventricular arrhythmias during not only acute myocardial ischemia [25] but also ischemia reperfusion [26]. Low-intensity atrial GP stimulation also caused a significant increase in vagal tone and an evident decrease in sympathetic tone as evaluated by heart rate variability and prevented the loss of connexin43 induced by ischemia/reperfusion [26]. These results indicate that atrial GP exert a protective role in acute myocardial ischemia.

Evidence for atrial GP denervation caused by heart failure

Recently, Shinohara et al. [27] used a radiotransmitter to record nerve activities from right stellate ganglion (sympathetic), right vagus nerve (parasympathetic), and right atrial GP in healthy control and pacing-induced heart failure dogs. They found that stimulating the superior right atrial GP in isolated right atrium significantly reduced the sinus rate in normal but not the heart failure hearts. Immunohistochemical staining showed significant lower densities of tyrosine hydroxylase- and choline acetyltransferase-positive nerve tissues in heart failure right atrial GP. These observations provoke the excitement for therapies targeted at stimulating the atrial GP in heart failure.

The applications ensure the feasibility and safety of atrial GP stimulation

Stimulation of the inferior right atrial GP has been reported to improve heart rate control in atrial fibrillation [28,29]. Mischke et al. [28] performed inferior right atrial GP stimulation via a cardiac neurostimulator in nine mongrel dogs and continuous neurostimulation was delivered for 1–2 years to decrease the ventricular rate during rapid atrial pacing-induced atrial fibrillation to a range of 100–140 bpm. The result showed that continuous neurostimulation was a safe, effective and well tolerated approach in the long term. Bianchi et al. [29] also validated this approach in humans both acutely and during follow-up. No significant change in pacing thresholds was observed after 3 months. These results provided data for the development of device-based control of ventricular rate during atrial fibrillation.

Besides ventricular rate control in atrial fibrillation, atrial GP stimulation was found to significantly reduce inflammatory cytokines in the postoperative period [30]. In 27 patients who were candidates for off-pump surgical revascularization, inferior vena cava-inferior atrial GP burst stimulation was performed for 6 h which induced significant reduction of interleukin-6, tumor necrosis factor-α, vascular endothelial growth factor and epidermal growth factor when compared with control patients.

Although the experimental and clinical studies mentioned above primarily employed screw-in leads attached to the inferior right atrial GP for stimulation, the anterior right atrial GP could also be chosen as the target. In a recent clinical study, Calò et al. [31] reported that the anterior right atrial GP could be stimulated and ablated with electrode catheter in the right atrium, providing the evidence for the feasibility of using screw-in leads to stimulate the anterior right atrial GP. To facilitate the attachment of an appropriate screw-in lead, one could use the Select Secure 3830 screw-in lead (Medtronic Inc., Minneapolis, Minnesota) within a deflectable sheath for attachment to the anterior right atrial GP.

The potential advantages of atrial GP stimulation

Although vagus nerve stimulation has been shown as an effective therapy for human heart failure [15,16], cervical surgery is needed to position vagal stimulation electrode. Besides, vagus nerve stimulation may also cause some undesired side effects such as cough, voice alteration, dyspnea, pain, paresthesia, headache [32], due to the relatively extensive innervation area of vagus nerve and the concomitant of the carotid artery. In contrast, atrial GP stimulation, especially performed endocardially via intravenous approach, would solve the problems encountered by vagus nerve stimulation. Another potential advantage of atrial GP stimulation over vagus nerve stimulation is that atrial GP is more localized to the heart itself and atrial GP stimulation could avoid some undesired systemic side effects, enhancing its efficacy. It should be pointed out that endocardial atrial GP stimulation for the treatment of heart failure is a minimally invasive treatment approach, just like a pacemaker implantation, which can be performed easily and safely. Although a surgical implantation of the stimulus generator is needed for both vagus nerve stimulation and atrial GP stimulation, the degree of injury induced by placing atrial GP stimulation leads is much less than that induced by positioning vagal stimulation electrode.

Consequence of the hypotheses

Sudden cardiac death is an important cause of mortality in the heart failure population, of which more than 75% is associated with ventricular tachyarrhythmia [33]. Due to a series of our recent studies [24–26], one potential therapeutic effect of atrial GP stimulation in heart failure would be the prevention of malignant ventricular arrhythmias. As inflammatory reaction plays an important role in the progression of chronic heart failure, the anti-inflammatory effect of atrial GP stimulation [30] further supports its therapeutic role in heart failure. Of note, the therapeutic effects of atrial GP stimulation may also be derived from its anti-adrenergic effect, both centrally and peripherally. Increasing parasympathetic activity as well as inhibiting sympathetic activity by atrial GP stimulation will be helpful to reverse autonomic dysfunction and augmenting the beneficial effects.

Conclusion

Recent clinical studies confirmed the therapeutic role of vagus nerve stimulation for heart failure. Our recent experimental
studies showed that atrial GP stimulation increased parasympathetic tone and decreased sympathetic tone as well as prevented the occurrence of ventricular arrhythmias during acute myocardial ischemia. We hypothesize that atrial GP stimulation may be feasible, safe and efficient for the treatment of heart failure, which takes potential advantages over vagus nerve stimulation. If supported by further experiments, our hypotheses would serve as a new strategy for the therapy of heart failure.

Conflict of interest

There is no conflict of interest to disclose.

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