

Effect of Low-Level Electrical Stimulation of the Aortic Root Ventricular Ganglionated Plexi on Electrical and Structural Remodling in Dogs with Heart Failure

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Abstract

Low-level electrical stimulation (LL-ES) of aortic root ventricular ganglionated plexi (GP) was proved to be antiarrhythmic in the initiation of AF mediated by autonomic nervous system. However, it is still uncertain whether LL-ES of the ventricular GP can reverse the structural remodeling of myocardial fibrosis and atrial enlargement following heart failure by attenuating the sympathetic tone. Therefore, this review will give an general argument on this topic.

The rise of vagal tone facilitated the activity of pulmonary veins and played an important role in the initiation of AF [1]. Autonomic nerve stimulation shortens AERP, decreases the wavelength of atrial reentrant circuits and increases dAERP, thus, promoting the stability of AF [2]. Several studies have demonstrated that additional ablation of epicardial ganglionated plexi (GP) improved success rate in catheter ablation of AF after circumferential isolation of pulmonary veins [3,4]. But in long term follow-up, the effect of GP ablation is limited due to high recurrence rate of AF [5,6].

As for more than a century, basic scientists had used strong vagal stimulation, which slowed the heart rate or caused sinus arrest, as a method for inducing AF. Recently, Li et al. gave a novel idea that low-level electrical stimulation (LL-ES) of vagal nerve VNS could suppress AF by inhibiting the intrinsic cardiac autonomic nervous system (ANS) and prevent episodic AF caused by rapid pulmonary vein and non-pulmonary vein firing [7]. Following Li's study, increasing evidences suggested that LL-ES of vagal nerve, with voltage levels 10-50% below threshold showed an antiarrhythmic effect [8-10]. Recently, Stavros Stavrakis [11] applied LL-ES skill to treat patients with paroxysmal atrial fibrillation, and they demonstrated that transcutaneous LL-ES suppresses AF and decreases inflammatory cytokines in patients with paroxysmal AF. These results indicated LL-ES of autonomic nerve could bring both anti-arrhythmia and anti-inflammation effect.

Since intrinsic ANS are mainly connected by some GPs that located in the epicardial fat pads. Previous study proved that epicardial GP could be anatomically divided into the atrial and ventricular GP, and the ventricular GP mainly innervated the ventricle and

coronary artery [12]. Moreover, He et al. found that the activity of atrial GP influenced the electrophysiology of the ventricle and ventricular arrhythmogenic properties as well [13,14]. These results indicated that the atrial and ventricular GP may cooperate with each other and act as a single functional unit. Therefore, we proposed that modulation of the ventricular GP would also affect the electrophysiology of the atrium. Our recent study demonstrated that stimulation of aortic root ventricular GP provoked robust AF in the absence of extrinsic cardiac nerve activity using an isolated perfused heart model [15]. These findings suggested that ventricular GP innervated PVs and contribute to the initiation of AF with the exception of atrial GP. Moreover, our latest studies showed that LL-ES of the aortic root ventricular GP attenuated the tension of autonomic nerves and reduce the occurrence of AF mediated by autonomic nervous system, which demonstrated the antiarrhythmic effect of LL-ES of the aortic root ventricular GP [16].

Because arrhythmia, especially AF is one of the complications accompanied with HF. AF induces atrial enlargement and electrical remodeling, which aggravates HF. It has been revealed that myocardial fibrosis and electrical remodeling resulted from high sympathetic tone offered an essential substrate for the development and maintenance of AF [17,18]. Previous studies also proved that modulation of vagal tone can reverse electrical or functional remodeling of HF. Li stated that vagal nerve stimulation can modulate the inflammatory response and affect specific inflammatory mediators including nitric oxide that may be contributory to continued or progressive heart failure [19]. Therefore, vagal nerve stimulation may present beneficial effects that are independent from heart rate or AV conduction in

heart failure. Kobayashi et al. found that endovascular cardiac GP stimulation induced significant and selective increases in left ventricle contractility without increasing heart rate [20]. Efforts to optimize electrode placement and fixation will improve the reproducibility of endovascular cardiac GP stimulation. These studies demonstrated that the decrease tone of ANS could also benefit to the treat of HF. It is therefore plausible to hypothesize that LL-ES of the aortic root ventricular GP would be antiarrhythmic and anti-inflammation, which might reverse the structural remodeling of myocardial fibrosis and atrial enlargement following HF by attenuating the sympathetic tone.

Therefore, our further study will use programmed electrical stimulation, burst electrical stimulation, immunohistochemistry, PCR and Western Blot, Ellesa, and patch clamp skills to determine the following data's. First, bioactive factors for HF, such as angiotensin II, TGF- β , mitogen-activated protein kinase (MAPK), matrix metalloproteinase (MMP) and tissue inhibitors of matrix metalloproteinase (TIMP) will be assessed to explore whether long-term LL-ES of the aortic root ventricular GP is capable of reversing the structural remodeling of the heart and help to treat HF. Second, ventricular effective refractory periods (VERPs), the dispersion of VERP and the inducing rate of arrhythmia by programmed electrical stimulation will also be measured to determine whether long-term LL-ES of the aortic root ventricular GP would improve the electrophysiological properties of the ventricle and get an antiarrhythmic effect.

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