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Cardiac neural remodeling and its role in arrhythmogenesis

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Cardiac innervation comes from both extrinsic and intrinsic sources. The extrinsic sympathetic innervation arises from the stellate ganglia and paravertebral sympathetic ganglia. The vagal nerves are sources of extrinsic parasympathetic nerves that innervate the heart. In addition to the extrinsic cardiac nervous system, there is also an extensive intrinsic cardiac nervous system¹ that includes collections of ganglionated plexuses (or “ganglionated plexi”, or GP). Each GP contains both sympathetic and parasympathetic neurons that are associated with complex synaptology. In addition to efferent nerves, the GP also contains afferent nerves. While GP at different locations of the heart have different specialized functions (such as controlling sinoatrial node, atrioventricular node etc), they are also known to communicate among each other and with the extrinsic nervous system.

Neural Remodeling and Cardiac Nerve Sprouting

The cardiac nerves are highly plastic and can respond to injury with denervation, nerve sprouting, partial reinnervation and even regional or global hyperinnervation.² Nerve sprouting and regionally heterogeneous sympathetic hyperinnervation work synergistically with structural remodeling and electrophysiological remodeling to reshape and reform the heart. The benefits of cardiac reinnervation are best demonstrated in patients with orthotopic cardiac transplantation.³ In those patients, partial sympathetic reinnervation after cardiac transplantation enables an increased peak oxygen uptake during exercise. This is most probably due to partial restoration of the chronotropic and inotropic competence of the heart as well as an improved oxygen delivery to the exercising muscles and a reduced ventilation-perfusion mismatching. However, nerve sprouting is also associated with detrimental side effects, such as ventricular arrhythmia and sudden cardiac death.² The mechanisms of cardiac nerve sprouting and sympathetic hyperinnervation are not entirely clear. However, one of the most likely mechanisms is the release or synthesis of multiple neurotrophic factors by the damaged myocardium.⁴ These neurotrophic factors are then retrogradely transported to the extrinsic or intrinsic ganglia, causing axonal nerve sprouting. The nerve sprouting is not specific to the site of injury. Rather, a small to moderate sized infarction of the left ventricle can cause nerve sprouting and sympathetic hyperinnervation of both ventricles, atria and even the sinoatrial node.⁵ The increased amount and heterogeneity of sympathetic nerves may be beneficial in

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maintaining myocardial contraction, but can also contribute to cardiac arrhythmogenesis. Beta blocker therapy is antiarrhythmic probably because it attenuates the arrhythmogenic effects of heterogeneous sympathetic hyperinnervation.

Nerve Discharges and Cardiac Arrhythmia

To better understand the relationship between nerve discharges and cardiac arrhythmia, we performed continuous recordings from ambulatory dogs 24-hr a day, 7-days a week to determine what is the normal patterns of cardiac nerve discharges. We found that the vast majority of cardiac nerve discharges are low amplitude burst discharges (LABDA), similar to normal brain waves. However, high amplitude spiky discharges (HASDA) are also routinely observed.⁶ HASDA usually occurs along with LABDA, but is more arrhythmogenic than LABDA. In dogs with both complete atrioventricular block and myocardial infarction, HASDA frequently causes premature ventricular contractions or even ventricular tachycardia (Figure 1). These findings suggest that HASDA is highly arrhythmogenic in diseased hearts. However, because HASDA is also present in normal hearts, the presence of these types of discharge by itself is not pathological. Choi et al⁷ adapted these recording techniques to study the nerve discharges in the GPs in ambulatory dogs. The authors found a significant temporal relationship between the activities of the extrinsic cardiac nerve structures (stellate ganglion and vagal nerves) and the intrinsic cardiac nerves (GPs). However, in a minority of incidences, the intrinsic cardiac nerve activity (ICNA) from the GPs can activate alone without being associated with the activities of the extrinsic nervous system. All paroxysmal atrial tachyarrhythmia episodes were invariably preceded by ICNA. These findings suggest that ICNA (either alone or in collaboration with extrinsic nerve activity) is an invariable trigger of paroxysmal atrial tachyarrhythmias.

Functional Specialization of the GPs

The complex function of the heart is controlled by a complicated array of nerve structures. It is a common knowledge that sympathetic and parasympathetic branches of the cardiac nerves have specialized functions. In addition, the GP located at different parts of the heart also have their own specialized functions. The right atrial (RA) GP located in the RA ventral fat pad, is near the sinoatrial node. It is not surprising that it controls the rate of the sinoatrial node. The atrioventricular node conduction is regulated by the inferior vena cava-left atrium fat pad. Both of them connect to a third fat pad at the superior vena cava and aortic root fat pad and the vagal nerve.⁸ Elimination of the fat pads with radiofrequency catheter ablation selectively vagally denervates the atria and sinoatrial and atrioventricular nodes. The anatomical proximity of the superior left ganglionated plexi to the left superior pulmonary vein-left atrial junction suggests that it may be involved in the induction of paroxysmal atrial tachycardia or atrial fibrillation (AF). This latter hypothesis is supported by ICNA recordings in a canine model of AF.⁷ While extensive communications are present between GP and between intrinsic and extrinsic nervous system, it is also possible for the GPs to activate alone without being triggered by extrinsic nervous system.⁷ In some incidences, GP activation alone (without the simultaneous activation of stellate ganglion or vagal nerves) can induce paroxysmal atrial tachyarrhythmias.

Future Directions

If extrinsic and intrinsic nerve activities are causally related to the initiation of AF, then ablation of these nerve structures should effectively prevent the recurrences of this arrhythmia. Recent clinical findings seem to support this hypothesis.⁹ However, others have shown that dissection of the superior vena cava and aortic root fat pad in patients undergoing cardiac surgery does not prevent postoperative AF.¹⁰ The lesson learned from the latter study is that we still do not fully understand the relationship between various GPs and cardiac arrhythmogenesis. A more detailed understanding of the functional subspecialization of the GP is needed for proper

identification of the most ideal targets for GP ablation. Furthermore, if GP activation is causally related to cardiac arrhythmogenesis, then reducing or modulating GP activation may be a novel target of pharmacotherapy. GP is also involved in heart rate control. Previous studies showed that sinoatrial node ablation does not cure inappropriate sinus tachycardia, suggesting that the problem may be more upstream. Reduced GP nerve activity could result in persistent tachycardia due to an absence of the mechanism that counterbalances the sympathetic discharges. If so, then the real therapeutic target for inappropriate sinus tachycardia is the GP, not the sinoatrial node.

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Figure 1.

Stellate ganglion nerve activity and ventricular tachycardia. This tracing came from a dog with anterior wall myocardial infarction and complete atrioventricular block.⁶ Intermittent HASDA (arrows) was followed immediately by a ventricular premature contraction (VPC) or an episode of nonsustained ventricular tachycardia (VT). In contrast, an episode of LABDA (asterisk) was not followed by any significant change of ventricular rate.