The heart and its nerves: A nervous bond

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It is well known that the heart is under tight autonomic control.1 The hierarchy includes the central nervous system, cervical stellate, intrathoracic ganglia, and intracardiac ganglionic plexuses in the epicardial fat pads. Anatomically, the cardiac autonomic hierarchy is divided into extrinsic cardiac nerves (ECN), mainly consisting of somata from the brain and the spinal cord and their projecting axons (i.e., vago-sympathetic trunks) physically located outside the heart, and intrinsic cardiac nerves (ICNs), consisting of somata and their axons physically located on the heart, with sympathetic neurites coursing subepicardially along the coronary vessels and parasympathetic neurites coursing subendocardially after traversing the AV groove.1,2 Ontogenically, ICN neurones appear in early fetal stage before the ingrowth of nerve fibers extrinsic to the heart, indicating they are two distinct systems.3,4 However, the two nervous systems are functionally interdependent but are capable of operating independently. It has been shown in canines that ICN neurones have spontaneous activities, entrained to cardiac and respiratory cycles but decreased after decentralization.5 The complexity of the ICN network is signified by its large number of neurones and transmitters. A young human heart may have more than 94,000 neurones and an adult heart more than 43,000, forming the most complex neuronal network outside the central nervous system.6 These neurones include adrenergic and parasympathetic postganglionic efferent neurones, afferent (sensory) neurones, and a large number of local circuit neurones. Besides catecholamines and acetylcholine, a large number of neuromodulators, including substance P, calcitonin gene-related peptide, and angiotensin II, are richly co-localized in local circuit neurones in the ICN,1 pointing to extensive interactions and modulations within the network,7 consistent with the findings of local circuit neurones being both intraganglionic and interganglionic.8 Because both the efferent and afferent somata and neurones are found in the networks, the heart and its nerves undoubtedly are tightly bonded, functioning like a control system, probably as a multior-der stochastic control system5 to ensure stable beat-to-beat control of the heart as it endures a wide range of demands ranging from sleeping to 100-meter sprinting.

Under physiologic conditions, sympathetic inputs to the heart produce positive chronotropic (rate), dromotropic (conduction), inotropic (contractility), and lusitropic (relaxation) effects through beta-stimulation and its activation of the G-proteins; parasympathetic inputs produce opposite effects.1 Although the core tenet of this sympathovagal balance hypothesis is the central arterial baroreflex, which may require the acid-sensing ion channel (ASIC2) to be a possible pressure sensor as shown in ASIC2 null mice,10 a large amount of evidence is accumulating that various reflexes exist at the different levels/parts of the ECN and ICN networks.7 Arrhythmias may result as sympathovagal imbalance ensues due to altered reflexes at some level of the ECN and/or ICN networks following the development of structural heart disease.

For atrial tachyarrhythmias, especially atrial fibrillation (AF), both sympathetic and parasympathetic nerves are implicated in the onset of arrhythmias. In humans, the occurrence of atrial fibrillation follows variation of autonomic activities, with the initial augmentation of sympathetic tone followed by an abrupt shift toward vagal predominance.11 A similar phenomenon was observed in a dog AF model with pacing-induced heart failure. Bilateral cryoablation of the stellate and T2–T4 thoracic ganglia significantly reduced the occurrence of atrial tachyarrhythmia.12 However, studies of ICN ganglionic plexuses suggest that increased vagal inputs are of more importance,13 and ablation of the vagal ganglia during pulmonary isolation helps terminate AF and maintain sinus rhythm in AF patients.14 Different from the initiation of AF, sympathetic hyperactivity is the predominant change in the autonomic nervous system preceding malignant ventricular arrhythmias. An increase of central sympathetic outflow, plasma norepinephrine level, and cardiac norepinephrine spillover (rising as high as 50-fold of control) have been reported in heart failure patients.15 Beta-blockade has been the mainstay of heart failure treatment. In the case of myocardial infarction, studies in a canine model have shown that denervation occurs in the infarcted areas, and heterogeneous sympathetic innervation with hypersensitivity at noninfarcted areas also takes place.16,17 More recently, it has been shown
that nerve sprouting occurs at both infarcted and noninfarcted areas, but to a different degree. These heterogeneous neuronal changes result in heterogeneity of ventricular refractory period and, therefore, substrates of reentrant ventricular arrhythmia. Ventricular arrhythmia is one of the main causes of sudden cardiac death in diseased hearts. With substrates of ventricular arrhythmia present in heart failure and postmyocardial infarction patients, the mechanisms of initiating ventricular arrhythmia are of great importance clinically. Premature ventricular contractions have been long considered to be a trigger for subsequent fatal ventricular arrhythmia. In this issue of Heart Rhythm, Smith et al present data on the effects of high-frequency ventricular ectopy on sympathetic neural activity in humans in order to assess the feedback of the heart to its nerves. In this well-designed study, the authors examined postganglionic muscle sympathetic (peroneal) nerve activity, coronary sinus norepinephrine level, and their correlation following induced high-frequency ectopy. It is shown that high-frequency ventricular ectopy promoted higher sympathetic neuronal activity. This increase in sympathetic neural activity correlated with coronary norepinephrine level to a good degree. These findings indicate that ectopic activities in the heart may have a “positive feedback” on sympathetic nerves. The increase in sympathetic neuronal activity due to this “positive feedback” would then promote further cardiac instability, causing fatal arrhythmias.

If this hypothesis holds, block of this “positive feedback” would be highly desirable in the prevention of fatal ventricular arrhythmia. Therefore, a question to be answered is how increased ectopic activities in the heart “feed back positively” to the sympathetic nerves. In their article, Smith et al propose that the baroreflex, which operates as a negative feedback system due to blood pressure decreases during ectopic activities, may account for the effects. However, what role did the ICN play? In other words, can afferent neurons in the ICN network feed back the changes in the heart during high-frequency ectopy to the ECN to accentuate sympathetic activities? A possible afferent mechanism is mechanosensitive feedback. The heart has mechanosensory neuritis, and some of its ion channels are mechanosensitive. It is thought that direct transduction of cardiac mechanical events, probably through deformation of sensory neurites in the ventral right ventricular papillary muscle, to cardiac motor neurons may represent an unstable feedback mechanism. Does the same apply to the feedback pathways into the peripheral sympathetic nerves during ventricular ectopy? Elucidation of this pathway and its modulation would potentially provide additional means to prevent sudden cardiac death as an adjunct to the beta-blockers used for blocking the inputs of extrinsic cardiac sympathetic nerves to the heart.

References