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Heart-brain interactions in cardiac arrhythmias: Role of the autonomic nervous system

■ **ABSTRACT**

The autonomic nervous system plays an important role in the genesis of ventricular arrhythmias and sudden cardiac death. Evidence is substantial for a neural component in sudden cardiac death. Sympathetic nerve sprouting and regional myocardial hyperinnervation following myocardial injury promote cardiac arrhythmia and sudden cardiac death through several potential mechanisms. Modulating autonomic tone is a potential method to reduce the risk of ventricular arrhythmias. Thoracic spinal cord stimulation is showing promise as a treatment for refractory angina. In addition, spinal cord stimulation has protected against ventricular tachycardia/ventricular fibrillation in animal models of postinfarction heart failure.

The autonomic nervous system has an important role in the genesis, maintenance, and interruption of ventricular arrhythmias.[1] In most instances, sympathetic activation precipitates or enhances ventricular arrhythmias, whereas vagal tone suppresses their occurrence.[2,3] Therefore, modulating autonomic tone has been proposed as a method to potentially suppress ventricular arrhythmias.[4]

An important mechanism underlying the development of ventricular arrhythmias is electrophysiologic heterogeneity. Electrical heterogeneity predisposes to the development of reentrant arrhythmias and other types of arrhythmias.[5]

■ **SYMPATHETIC AND PARASYMPATHETIC INNERVATION OF THE HEART**

Sympathetic nerve fibers are located subepicardially and travel along the routes of the major coronary arteries. In contrast, the vagus nerve is subendocardial in its location after it crosses the atrioventricular groove. A lesion of the heart produced by infarct or fibrosis can result in denervation of otherwise normal myocardium by interruption of neural axons traveling through the lesion. A defect in sympathetic function following myocardial infarction (MI) has been demonstrated in both animals and humans as measured by iodine-123-metaiodobenzylguanidine (MIBG) and C-11 hydroxyephedrine.[6]

Reduced uptake of MIBG in the inferior wall has recently been observed in patients with idiopathic ventricular fibrillation as compared with controls. Although no difference in survival could be detected between the two groups, patients with reduced uptake of MIBG had an increased incidence of ventricular tachyarrhythmias compared with those who did not have such a defect.[7]

Similar observations of sympathetic dysfunction have been made in a variety of animal models and humans with heart failure, coronary disease, and ventricular tachycardia in the absence of structural heart disease. In such instances, the speculation is that sympathetic heterogeneity may produce electrical heterogeneity and spur the development of ventricular arrhythmias. The arrhythmic mechanism is probably more complex than this description, however, because the response to sympathetic inhibition using beta-blockers is not uniform.

Evidence of nerve sprouting
Using a growth-associated protein antibody that marks axonal growth, nerve sprouting has been demonstrated in mice in areas of denervation following MI.[8] Similarly, using growth-associated protein 43 staining, researchers have demonstrated nerve sprouting in the right atrial free wall, right atrial isthmus, and right ventricle in dogs after radiofrequency catheter ablation.[9]

Neural component in ventricular arrhythmias
Sympathetic hypersensitivity has been shown in areas of denervation, which may be related in part to nerve sprouting. Other sympathetic and electrical phenomena following myocardial injury include an upregula-

tion of nerve growth factor, a heterogeneous distribution of sympathetic innervation, and electrical heterogeneity with areas of denervation, hyperinnervation, and normal nerve density.

Two discoveries by Chen and colleagues are perhaps most noteworthy. One is that nerve growth factor infusion and stellate ganglion stimulation following MI increase nerve density and ventricular arrhythmias, with increased burst frequency discharge of the stellate ganglion prior to the onset of ventricular tachycardia/ventricular fibrillation (VT/VF) in dogs.[8] More recently, they have shown that infusion of nerve growth factor into the stellate ganglion prolongs the QT interval and prolongs ventricular arrhythmias.[10]

A relationship has been established between the hyperinnervation that occurs following myocardial injury and ventricular arrhythmias. Using immunocytochemical staining in explanted native hearts of transplant recipients, Chen and colleagues demonstrated colocalization of Schwann cells, sympathetic nerves, and nerve axons, as well as regional cardiac hyperinnervation, with the most abundant nerve sprouting in the areas bordering myocardial injury and normal myocardium.[8] In addition, they demonstrated positive tyrosine hydroxylase staining of cardiac nerves in areas around coronary arteries in patients with coronary disease and idiopathic dilated nonischemic cardiomyopathy. At the origin of ventricular tachycardia (prior to transplant), nerve sprouting was shown by staining for S100 protein and tyrosine hydroxylase. The authors hypothesized that nerve sprouting may give rise to ventricular arrhythmia and sudden cardiac death, in which MI results in nerve injury, followed by sympathetic nerve sprouting and regional myocardial hyperinnervation.[10]

A link with circadian variations in QT interval length?
The observation that nerve growth factor infused into the left stellate ganglion prolongs the QT interval and prolongs ventricular arrhythmias, resulting in an inordinate risk of sudden death, is fascinating in the context of recent findings of a circadian variation in duration of the QT interval. In measuring QT intervals in 3,700 men without ventricular arrhythmias, we found that the QT interval peaked in winter (between October and January), with a 6-msec difference between the longest and shortest QT intervals.[11] This increase in the QT interval in winter coincides with an increase in the incidence of sudden death, which occurs in many regions of the world regardless of climate. Whether or not this increase in sudden death in winter is related to a longer QT interval is supposition, but the potential

interaction deserves further exploration. A similar surge in sudden death in winter was observed in patients who were eligible for an implantable cardioverter-defibrillator (ICD) but did not receive one, as opposed to those who did receive an ICD, which suggests that the mechanism responsible for the increase in sudden death in winter is a ventricular tachyarrhythmia that can be prevented by an ICD.[12]

How sympathetic hyperinnervation promotes cardiac arrhythmias is speculative, but increased density of sympathetic nerve endings could promote the release of sympathetic neurotransmitters during sympathetic excitation. The autonomic remodeling is associated with heterogeneous electrical remodeling of cardiomyocytes, resulting in prolongation of action potentials in hyperinnervated regions. Further, acute release of sympathetic neurotransmitters probably accentuates the heterogeneity of excitability and refractoriness, likely contributing to arrhythmia susceptibility.[5]

■ PHARMACOLOGIC SYMPATHETIC BLOCKADE
Inhibiting sympathetic activity pharmacologically reduces the incidence of sudden cardiac death in patients with heart failure. In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), the aldosterone inhibitor eplerenone was associated with a clear reduction in sudden cardiac arrest in patients with acute MI complicated by left ventricular dysfunction.[13] Beta-blockers and angiotensin-converting enzyme inhibitors have had the same effect. These findings indicate that adverse electrophysiologic consequences from sympathetic stimulation may contribute to the development of a proarrhythmic substrate, and that antagonizing sympathetic activation can reduce the extent of adverse electrical remodeling to reduce the risk of sudden cardiac death.

■ SPINAL CORD STIMULATION
Acute spinal cord stimulation
The possibility of using spinal cord stimulation to modulate cardiac arrhythmias is intriguing, as electrodes introduced paraspinally may activate nerves that could affect sympathetic function. In Europe, spinal cord stimulation is already approved for treatment of patients with intractable angina and end-stage coronary disease.

The mechanism responsible for elimination of angina pectoris via carotid sinus massage is presumably an increase in vagal activity to the heart. In a study of whether thoracic spinal cord stimulation eliminates angina pectoris via a vagal mechanism, Olgin et al confirmed that spinal cord stimulation at the T1-T2 segments enhanced parasympathetic

activity and that this action is mediated via the vagus.[14] These findings suggest that thoracic spinal cord stimulation may protect against ventricular arrhythmias through its effect on autonomic tone.

This suggestion led to the development of a canine model of spontaneous ventricular arrhythmias to investigate the mechanisms responsible for ventricular arrhythmias related to acute myocardial ischemia in the setting of healed MI.[15] An infarct was produced via occlusion of the left anterior descending coronary artery and a permanent ventricular pacemaker was placed. After a 2-week recovery period, heart failure was induced by continuous rapid ventricular pacing for 2 to 3 weeks. Transient myocardial ischemia was induced by transient occlusion of the proximal left circumflex coronary artery. Seventy-two percent of dogs surviving the rapid pacing period developed VT/VF during acute left circumflex artery occlusion or within 1 to 2 minutes thereafter.

The effect of thoracic spinal cord stimulation applied at the dorsal T1-T2 segments was studied on the surviving dogs.[16] Spinal cord stimulation reduced the occurrence of VT/VF from 59% to 23%.

Another study examined the effect of intrathecal clonidine, an alpha-2 antagonist that reduces concentrations of catecholamines, on ventricular arrhythmias in the canine model.[17] Ischemia-induced VT/VF occurred in 9 of 12 dogs before administration of intrathecal clonidine in contrast to only 3 of 12 dogs after clonidine administration, a degree of efficacy similar to that with spinal cord stimulation.

Chronic spinal cord stimulation

Studies of the effects of chronic thoracic spinal cord stimulation on ventricular function and ventricular arrhythmias in a canine postinfarction heart failure model have recently been completed, and the results will be published in the near future.[18]

■ CONCLUSIONS

Sudden cardiac death continues to be a major health problem in Western countries. Many approaches have been explored in attempting to reduce this modern-day plague.[19] A better understanding of the risks, mechanisms, and treatments is required.[20] An animal model has demonstrated that acute modulation of autonomic tone with thoracic spinal cord stimulation or intrathecal clonidine reduces susceptibility to ischemic ventricular arrhythmias, presumably via a sympatholytic mechanism. Modulation of autonomic tone—sympatholytic, vagomimetic, or both—may play a significant role in protecting against spontaneous and ischemic ventricular tachyarrhythmias.

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