Treatment of Arrhythmias and HF With Autonomic Modulation

Written by Mary Mosley

The connection between the brain and the heart is supported by the description of arrhythmias associated with the central nervous system, stated Peng-Sheng Chen, MD, Indiana University, Indianapolis, Indiana, USA. These include arrhythmias that occur in relation to seizure disorders, sudden unexpected death in epilepsy (SUDEP), congenital long-QT syndrome (LQTS) in patients with genetic arrhythmias, and stress cardiomyopathy. Dr. Chen and colleagues are working to develop noninvasive methods to assess sympathetic tone through sensors on the skin to assist with better describing and possibly even preventing these types of arrhythmic events.

Seizure activity elevates sympathetic tone and thus can be proarrhythmic, said Dr. Chen. Although sinus tachycardia (ST) is the most common cardiac arrhythmia during seizure, bradycardia has also been described in case reports [Carvalho KS et al. *Seizure* 2004]. An epidemiologic study published in 1985 found the prevalence of SUDEP in patients aged 14 to 21 years to be 5.7 per 100,000 person-years. Assuming a prevalence of epilepsy of 7 per 1000 persons, the relative risk of SUDEP was calculated to be 188.6 per 1000 persons with epilepsy and 4.6 per 1000 persons without epilepsy [Annegers JF, Coan SP. *Seizure* 1999].

Communication between the brain and the heart via the spinal cord, said Dr. Chen, is associated with ST, atrioventricular nodal conduction diseases, and sudden cardiac death (SCD) in patients with massively increased sympathetic output plus organic disease. A recent study showed that 13% of patients with SUDEP had a genetic variant that predisposed them to ventricular arrhythmias [Tu E et al. *Brain Path* 2011].

Abnormal findings on electroencephalography are more common in patients with LQTS (12 of 17 patients vs 2 of 16 controls) [Haugaa KH et al. *Heart Rhythm* 2013]. Although the relationship between LQTS and seizure disorders has been recognized, it is unclear which precipitates the other, and it may be that the disorders share some genetic mutations [Chen LS, Spoonamore K. *Heart Rhythm* 2013].

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The most accepted theory for the cause of stress-induced cardiomyopathy is the differential innervation of sympathetic nerves (SN) in the base of the heart [Lyon AR et al. *Nat Clin Pract Cardiovasc Med* 2008]. Excessive and prolonged sympathetic stimulation during stress leads to a negative inotropic effect because of activation of b_2 receptors, which are increased in number in the apical area secondary to reduced SN innervation.

LEFT CARDIAC SYMPATHETIC DENERVATION

Left cardiac sympathetic denervation (LCSD) has been shown to effectively treat ischemic arrhythmias, LQTS, and catecholaminergic polymorphic ventricular tachycardia (CPVT) and to prevent SCD after myocardial infarction (MI). Peter J. Schwartz, MD, Center for Cardiac Arrhythmias of Genetic Origin, IRCCS Istituto Auxologico Italiano, Milan, Italy, reviewed experimental and clinical data.

Historically, the description of a reflex excitation of the SN by acute myocardial ischemia, which resulted in ventricular fibrillation (VF) led to experimental work showing that LCSD through the blocking the left stellate ganglion reduced VF and SCD and could raise the threshold for VF by 70% without the use of drugs. LCSD also increased the ventricular refractory period, VF threshold, and myocardial reactive hyperemia.

The Italian Sudden Death Prevention Group study, conducted before beta-blockers were standard treatment for MI, showed that LCSD and oxprenolol had a similar lower rate of SCD (~3%) compared with placebo (~20%) for patients who had an MI with VF or ventricular tachycardia (VT). A recent retrospective analysis reported that LCSD or bilateral CSD in patients with cardiomyopathy and refractory VT or VT storms significantly reduced implantable cardioverter-defibrillator (ICD) shocks

(p<0.001); 30% of patients in the LCSD group and 48% in the bilateral CSD group had continued freedom from ICD shocks, and 90% of the patients had significant reductions in ICD shock burden [Vaseghi M et al. *Heart Rhythm* 2014].

In high-risk patients with LQTS, LCSD reduced any cardiac event by 91% and life-threatening events by 64% [Schwartz PJ et al. *Circulation* 2004]. Prior to treatment, 99% of the patients were symptomatic, 48% had experienced cardiac arrest, 75% had recurrences despite β-blocker use, and the mean corrected QT interval was 543±65 ms. The impact on ICD shocks is shown in Table 1.

Table 1. ICD Multiple Shocks and LCSD

Variable	Value
Patients with LCSD after ICD	5
Follow-up ICD before LCSD, months	17±16
Follow-up after LCSD, years	4.1
Pre-LCSD shocks per patient per year	29.3
Post-LCSD shocks per patient per year	3.3
Reduction	95%

ICD=implantable cardioverter-defibrillator; LCSD=left cardiac sympathetic denervation; LQTS=long-QT syndrome.

Source: Schwartz PJ et al. *Circulation* 2004.

CPVT is associated with a very poor quality of life because of the frequency of ICD shocks. The long-term efficacy of LCSD was first shown in 3 patients who had experienced life-threatening cardiac events and after a mean follow-up period of 8 years had a 90% reduction in major arrhythmic events [Wilde AAM et al. *N Engl J Med* 2008]. The multinational CPVT registry has shown that LCSD prevented, suppressed, or significantly reduced major cardiac events in 91% of 55 high-risk patients receiving optimal medical therapy. Prof. Schwartz recommended LCSD therapy in addition to β-blockers as a rationale approach for high-risk patients with CPVT, either alone or complementing ICDs used as a safety net.

NEUROMODULATION TO TREAT HEART FAILURE

Paul J. Wang, MD, Stanford University School of Medicine, Palo Alto, California, USA, reviewed experimental data that support human clinical trials of device-based neuromodulation in patients with heart failure (HF) to determine its safety and efficacy. The imbalance of parasympathetic and sympathetic systems in HF led to the hypothesis that modulating the autonomic nervous system would improve HF [Lopshire JC, Zipes DP. *Curr Cardiol Rep* 2012].

Sympathetic activation is compensatory in early HF but is deleterious in late HF, leading to decreased responsiveness of the myocardium to adrenergic stimuli [Lopshire JC et al. *Curr Cardiol Rep* 2012]. Changes in cellular processes such as abnormal calcium handling and apoptosis occur, and abnormal cardiac reflexes can develop, which suppress the inhibitory arterial baroreceptor reflex and enhance excitatory sympathetic afferent and arterial chemoreceptor reflexes. Decreased parasympathetic tone increased heart rate and decreased heart rate variability, correlated with increased mortality, and increased vagal afferent activation (eg, cardiac cytokine and neurohumoral activity) and was associated with changes in parasympathetic ganglionic signaling and a decrease in postganglionic muscarinic receptor density and function.

Experimental data for the benefit of spinal cord stimulation (SCS) and vagal nerve stimulation (VNS) were also reviewed. SCS at the T1 level delivered before and during coronary artery occlusion reduced infarct size, significantly increased the sinus cycle length and AH interval, and ischemia-mediated ventricular arrhythmias were reduced in a canine model [Lopshire JC, Zipes DP et al. *Curr Cardiol Rep* 2012]. Another animal study demonstrated a significant decrease in spontaneous and ischemic ventricular arrhythmias with SCS, medical therapy, or SCS plus medical therapy, compared with control. The SCS and the SCS plus medical therapy treatment groups also had significant improvements in resting heart rate, systolic blood pressure, and oxygen saturation, along with recovery of left ventricular ejection fraction (LVEF) and significant reversal of left ventricular (LV) dilatation. Two studies of SCS neuromodulation are under way in humans: the randomized, single-blind Determining the Feasibility of Spinal Cord Neuromodulation for the Treatment of Chronic Heart Failure trial [NCT01112579] for safety and efficacy in advanced HF and the nonrandomized Spinal Cord Stimulation For Heart Failure study [NCT01362725] in systolic HF.

VNS in experimental models reduced ventricular arrhythmias and mortality, slowed HF progression in a canine model, reduced heart rate, significantly improved LVEF, and reduced LV volumes. In combination with β-blocker therapy, VNS produced the greatest reduction in LVEF, decreased circulating cytokines and myocyte hypertrophy, and restored baroreflex control to normal [Lopshire JC et al. *Curr Cardiol Rep* 2012]. The Phase 2 Cardio-Fit trial [De Ferrari GM et al. *Eur Heart J* 2011] demonstrated that VNS significantly improved LVEF from 22% to 29%, reduced LV systolic volumes at 6 months, and improved quality of life. The Increase of Vagal Tone in CHF [NCT01303718], vagal Nerve Stimulation: Safeguarding Heart Failure Patients [NCT02113033], and Barostim Hope for Heart Failure [NCT01720160] studies of VNS are currently under way.