Autonomic Modulation as a Paradigm for Cardiovascular Treatments

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Atrial Fibrillation-GP Radiofrequency Ablation

Background: Four major ICANS GP are located on the atrial epicardial surface (see Figure). First discovered in the 1970s, these GP integrate extrinsic and intrinsic cardiac ANS with chronotropic, dromotropic and inotropic consequences. Relatively recently, radio frequency (RF) ablation of specific GP has been added to the usual ablation regimen of pulmonary vein isolation performed primarily by catheter or surgical techniques. Major GP have been implicated in AF. Balance between cardiac intrinsic and intrinsic ANS may be responsible for AF, especially in the aged. Such dystymia may be corrected by reducing GP tone. We have shown that an approach with less invasion and risk and cost can reduce GP activity. Targeting magnetic nanoparticles carrying neuromodulation drugs to GP has acutely prevented/suppressed AF in dogs.

Atrial Fibrillation-Vagal Nerve Stimulation

Background: Efferent vagal stimulation has previously been associated with termination of ventricular tachycardia (Warren, 1977), prevention of sudden cardiac death (cavale, Vanoli, 1991) and amelioration of heart failure. We have shown, however, low level vagal stimulation, below effective bradycardic effects, experimentally protects against AF (Singh et al., 2011). We reduced AF inducibility following stimulation of the vago-sympathetic trunk at either 1 V or 10-50% below threshold. The vagal complex provides two way communications and physiological-physiological pathophysiological information for the heart (Ardevoll, 2004). This paradigm may apply to other viscera as well.

Atrial Fibrillation: Magnetically Targeted Nanof ormulation

Background: Continuously variable external electromagnets are the optimal means of targeting magnetically susceptible nanoparticles for delivery of therapeutic substances to targeted tissues. The scientific teams of NTIS Inc. include physicians, engineers, clinicians, physiologists, pharmacologist/toxicologist, chemist and pathologist for the design and testing of an electromagnetic system for targeted delivery. We have proven the concept of magnetic targeting in the canine, using permanent magnets placed over the GP to target neurosuppressors. AF inducibility has been reduced (Yu, 2011). Continuing studies using external, variable electromagnetic fields have been capable of injection of magnetic-polymer-drug NP in coronary arteries and extracranial into atrial epicardium surrounding GP.

Vaso-Vagal Syncope-GP Ablation

Background: Different syncope syndromes are under the umbrella of vaso-vagal syncope. The central cardiovascular reflex and its short latency to consciousness. Clinical studies indicate that GP ablation prevents syncope episodes of vaso-vagal syncope. The central inhibitory response is decreased in HR, cardiac output and arterial pressure. This response is primarily from enhanced parasympathetic tone. But mechanisms underlying GP manipulation of V-VS are unknown. We hypothesize that V-VS may be due to an "epileptic type" burst of electrical activity in the medulla leading to a transient hyperactive state of the extrinsic autonomic nervous system. It is expected that GP ablation may result in an improvement in V-VS symptoms. Method: 10 anesthetized dogs, left and right cervical vagal trunks (LVG and RVG) were dissected; wires were electrode inserted for electrical stimulation. After thoracotomy, a plaque electrode was attached to the anterior and inferior right atrium (ARGP). Electrical stimulation at each site decreased HR by 50%. We determined the HR slowing induced by RVG+LVG, RVG+ARGP, LVG+ARGP and LVG+RVG+ARGP at voltages equal to and below the threshold required to initiate V-VS. Results: Average baseline HR was 130 beats/min. Combination of RVG+LVG induced a greater reduction in HR than RVG+ARGP (p=0.0002) or LVG+ARGP (p=0.0001) alone. RVG+ARGP and LVG+ARGP induced a greater than 65.9% and 71.8% HR reduction, respectively, than either RVG (p=0.0002) or LVG (p=0.0001). Combined RVG+L VG+ARGP induced the greatest (76.7%) change in HR (10 to 42/min) and preceding asymptotic periods of 3 to 7 seconds. Lidocaine injection into ARGP markedly attenuated the HR slowing and the associated V-VS. Conclusion: Combined stimulation of the Vagal trunks+ARGP models the cardioinhibitory form of VVS with a common pathway mediated through GP.

Atrial Fibrillation-Tragus Stimulation

Background: We recently have shown in canines and 40 patients that low-level transcutaneous electrical stimulation of the auricular branch of the vagus nerve at the tragus (LLTS), suppresses AF. The mechanism contains many related, divergent effects on the central autonomic nervous system. We examined if LLTS suppressed AF inducibility and duration, as well as decreased acute AF-related pressure and pro-inflammatory effects in patients with paroxysmal AF. Methods: 16 anesthetized dogs; electrodes attached to pulmonary veins and atria; microelectrodes inserted into anterior right GP; Rapid atrial pacing (RAP) induced atrial remodeling and AF tragus stimulation at 20 Hz at 80% below threshold for slowing sinus rate. Effective Refractory Period (ERP) was measured, the window of vulnerability decreased. Results: Blood samples were drawn from coronary sinus or femoral vein before and following 1 hr. of stimulation and analyzed for TNF-α, IL-1β, and intercellulin-6. Results: Dogs fast atrial pacing increased WOVD and decreased ERP. (P<0.05). LLTS returned ERP, WOVD and neural activity to baseline levels (P<0.05). AF duration decreased and AF cycle length increased after tragus stimulation. Conclusions: LLTS is a translatable therapeutic treatment for the prevention of AF. The LLTS group was not in control group. Systemic cytokines changed favorably only in the LLTS group.

Conclusion: ANS experimental maneuvers are emerging as a feasible alternative to pharmacological interventions paradigms for cardiovascular diseases.

Autonomic Modulation-Cardiac: Cather and surgical RF lesions of major GP can complement PVI RF lesions for the prevention of AF.

Autonomic Modulation-Experimental: Selective vagal stimulation, below the threshold of anesthetized GP, evokes a central ANS-mediated effect on the GP. The GP ablates and prevents AF.

Autonomic Modulation-Experimental: Neurosuppressant drugs, magnetically targeted to selected GP in nanoparticles, suppresses AF.

Vaso-Vagal Syncope-Experimental: GP ablation reduces GP activity. Targeting magnetic nanoparticles carrying neuromodulation drugs to GP has acutely prevented/suppressed AF in dogs.

Yu et al., Circ, 2011;