The Role of Autonomic Dysfunction in Arrhythmogenesis

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Goals of the Presentation

- Well known relationship between autonomic nervous system and arrhythmias
- More recently discovered relationships
  - Atrial fibrillation
  - Ventricular tachycardia
  - Sudden cardiac death
- Newer treatment modalities for arrhythmias relating to autonomic nervous system
The heart is a simple pump
Pump Timing is the Cardiac Rhythm and Timing Problems are Arrhythmias
Relation between the Autonomic NS and Cardiac Function

- Beneficial effects of beta-blockers on incidence of death post myocardial infarction
- Increase in MI with medications with anticholinergic properties
- Worse outcome in patients with CAD and depression
- Increase incidence of SCD in patients with post-traumatic stress disorder
Rich autonomic innervation

• Sinus node
• AV node
  – Exercise and stress ÷ HR and ÷ PR interval
  – Vagal effects during neurocardiogenic syncop
Autonomic Nervous System in the Post Transplanted Heart

• 64 y/o man s/p OHT 1989 who experienced syncope 12/04, cathed with significant transplant vasculopathy underwent single chamber ICD implant. (VVI 40)

• Episode of presyncope 2 years ago while on treadmill, interrogation showed no arrhythmia

• Underwent ICD generator change 1/09 due to battery depletion.
During pocket manipulation

- VVI pacing at 60 bpm
- Paced 481 times in 4 years!
- BP 72/56, feeling hot and sleepy
- Given 1 mg IV atropine
- HR 85, BP 118/78
Autonomic Nervous System Involvement

- Atrial fibrillation
- Ventricular tachyarrhythmias
- Sudden cardiac death
Atrial Fibrillation Affecting the Nervous System
Acetylcholine effects

• Increases atrial susceptibility to Afib
  - decreases action potential duration
  - increases dispersion of refractoriness
  - decreases wavelengths of reentrant circuits

• Potassium blocking AA drugs increase APD

• Surgical maze procedures damages autonomic fibers which may enhance its success rates
Induction of Atrial Fibrillation

- Holter tapes from 77 unselected pts with PAF
- 147 episodes
- Time domain and frequency domain HRV

PAF depends on variation in autonomic tone with a primary increase in adrenergic tone followed by an abrupt shift toward vagal predominance.

Triggers for Atrial Fibrillation

PVI and Autonomic Nervous System

- Parasympathetic nerve plexi located in LA and around pulmonary veins
- Reports of hypotension and bradycardia during ablation
- HRV alterations founds post PVI
- Vagal stimulation during ablation and vagal denervation post ablation probable causes
- “Pulmonary vein denervation”
Added benefit of Vagal Reflex Abolition

- 297 pts undergoing ablation for PAF
- Abolition of all evoked vagal reflexes around all PV ostia was obtained in 34.3% of pts
- 24 pts developed an inappropriate sinus tachycardia which lasted up to 1 month
- 12 months freedom from symptomatic AF
  - 85% of patients with vagal denervation
  - 99% of patients with vagal denervation and vagal reflex during ablation

Autonomic Nervous System and Ventricular Tachycardia

- Sympathetic fibers located subepicardially and travel along with major coronary arteries.
- Defect in sympathetic function post MI demonstrated in animals and humans by:
  - Iodine-123-metaiodobenzylguanidine (MIBG)
  - C-11 hydroxyephedrine
- Sympathetic heterogeneity may produce electrical heterogeneity leading to ventricular arrhythmias.
More Autonomic Nuances

- Mouse infarct model, nerve sprouting in areas of denervation using a growth-associated protein antibody that marks axonal growth
- Dog model with nerve sprouting post ablation
- Sympathetic hypersensitivity
  - Nerve sprouting
  - Upregulation of nerve growth factor
  - Heterogeneity of sympathetic innervation
The infarct border zone

- Using immunocytochemical staining in explanted hearts in pts undergoing transplant
- Co-localization of Schwann cells, sympathetic nerves and nerve axons
- Regions of cardiac hyperinnervation
- Most abundant nerve sprouting

Autonomic Therapies

- Beta-blockers
- Angiotensin converting enzyme inhibitors
- EPHESUS – aldosterone inhibitor eplerenone was associated with a reduction in SCD post MI
- Antagonizing sympathetic activation can reduce the extent of adverse electrical remodeling
Spinal Cord Stimulation

- Approved in Europe for treatment of intractable angina and end-stage CAD
- Spinal chord stimulation at T1-T2 segments has been shown to enhance parasympathetic activity via vagus nerve
- May be a role in ventricular tachyarrhythmias
Spinal Cord Stimulators
Animal Models

- Dog LAD infarct model 2 weeks, rapid pacing to produce CHF 2-3 weeks
- 72% survivors developed VT/VF during transient LCx occlusion
- Repeated LCx occlusion with and without spinal cord stimulation at T1-T2
- Occurrence of VT/VF decreased from 59% to 23%

Intrathecal Clonidine Post-Infarct Canine Model

- Intrathecal clonidine – treats neuropathic pain
- Causes hypotension and bradycardia
- 12 dogs, healed infarct model, EPS before and after Clonidine, randomized dogs saline or clonidine sequence
- Clonidine
  - 31% decrease HR
  - 22% increase in PR interval
  - 19% increase AERP
  - 9% increase VERP
- VT/VF incidence from 75% to 25% during ischemia

- Issa ZF et al., Heart Rhythm 2005;2:1122-7
Conclusions

- Autonomic nervous system is an integral part of cardiovascular system and cardiac arrhythmogenesis
- Pharmacologic options are limited
- Ablation strategies to target autonomic innervation of the heart are becoming commonplace
- Device therapies offer promise