Neural Control of Ventricular Rate in Ambulatory Dogs with Pacing Induced Sustained Atrial Fibrillation

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Brain-Autonomic Nerves and the Heart

National Disaster
-- SCD increases at times of national disaster

Experimental models
-- VS protects against stress induced arrhythmia
  Stress magnifies the proarrhythmic effects of ischemia

Humans
-- Stress induces coronary or microvascular constriction
  Anger potentiates ventricular arrhythmias
  Beta-blockade protective for SCD
  Emotion precipitates VF in long QT patients

Socioeconomic influence
-- Chronic psychosocial factors influence rates of arrhythmia
  and sudden death

Taggart P et al. BMJ 2010
Brain-Autonomic Nerves and the Heart

National Disaster
-- Earthquake

National Disaster
-- Terror

Role of adrenergic and cholinergic stimulation in spontaneous atrial fibrillation in dogs

Autonomic AF - Differentiation

• Adrenergic AF
  -- Tachycardia
  -- Postoperative
  -- Alcohol
  -- Exercise
  -- Emotional stress
  -- Polyuria
  -- Better with BB
  -- More common with heart disease

• Cholinergic AF
  -- Male predominance
  -- Age at onset 40-50
  -- Bradycardia
  -- Vomiting
  -- Severe constipation
  -- After large meal
  -- Cold carbonated beverages
  -- Rest
  -- Coughing
  -- Diving into cold water
  -- Valsalva
  -- Exacerbated with digoxin, beta-blockers
  -- More common without heart disease
Electrical and Structural Remodeling During Atrial Fibrillation

Anti-arrhythmic drug therapy for atrial fibrillation: current anti-arrhythmic drugs, investigational agents, and innovative approaches

A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation: Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr (n=969)</td>
<td></td>
</tr>
<tr>
<td>≥65 yr (n=3091)</td>
<td></td>
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<tr>
<td>Rhythm at randomization</td>
<td></td>
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<tr>
<td>Atrial fibrillation (n=1774)</td>
<td></td>
</tr>
<tr>
<td>Sinus rhythm (n=2000)</td>
<td></td>
</tr>
<tr>
<td>Type of episode of atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Recurrent (n=2590)</td>
<td></td>
</tr>
<tr>
<td>First (n=1501)</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>No (n=2590)</td>
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<tr>
<td>Yes (n=1501)</td>
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<tr>
<td>Hypertension</td>
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<td>No (n=1184)</td>
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<tr>
<td>Yes (n=1312)</td>
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<tr>
<td>Congestive heart failure</td>
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<tr>
<td>No (n=3121)</td>
<td></td>
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<tr>
<td>Yes (n=539)</td>
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<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
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<tr>
<td>&lt;50% (n=766)</td>
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<tr>
<td>≥50% (n=2244)</td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
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<tr>
<td>Female (n=1624)</td>
<td></td>
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<tr>
<td>Male (n=2468)</td>
<td></td>
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<tr>
<td>Duration of atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>≤2 days (n=3121)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 days (n=2809)</td>
<td></td>
</tr>
<tr>
<td>Overall (n=4030)</td>
<td></td>
</tr>
</tbody>
</table>

AFFIRM Investigators. NEJM 2002; 347:1825-33
Lenient versus Strict Rate Control in Patients with Atrial Fibrillation: RACE II

Van Gelder IC, et al. NEJM 2010; 362:15
What does AV node do?
What happens to AV node?

From patient’s EP strip
한강다리 폭파, 방실결절 절제

Photographs from google.com
AV node

“줄을 서시오”
AV Node
- Mystery of conduction delay -

Anatomy Atlases. Bergman RA.
Anatomy of the Extrinsic and Intrinsic Cardiac Nervous System

The Anatomical Record. Yuan BX et al. 1994; 239; 75-87
Selective innervation of SA and AV node and
Little brain of the Heart

Ardell JL et al. Am J Physiol
DC Randall et al. Am J Physiol
Direct evidence of nerve discharge and cardiac arrhythmia in ambulatory animal
Sympathovagal coactivation associated with rapid VR during AF

SGNA; Stellate ganglion NA, VNA; Vagal nerve activity
Intrinsic Cardiac Nerve Activity and Paroxysmal Atrial Tachyarrhythmia in Ambulatory Dogs

Purpose

- Relative importance of RVNA and LVNA
- Relation of IVC-IAGPNA and VNA
- Sole role of IVC-IAGPNA without VNA

IN AMBULATORY DOGS WITH PACING INDUCED SUSTAINED ATRIAL FIBRILLATION
Posterior view of the atria and GP

Operation view of the atria and GP

CW Chiou et al. Circulation 1997;95:2573-2584

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Methods

- Bilateral vagus nerve activity (VNA) and IVC – inferior atrial ganglionated plexus nerve activity (IAGPNA) recording during sustained (>48 hours) AF in ambulatory dogs.

- NAs were integrated over 10-s segments, resulting in 8640 data points/24 hours. We also determined the average VR during AF for that 10-s period.

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Methods – Study protocol

- Operation
- Repeat until the development of persistent (>48 h) AF
- Harvest

0 1 2 3 4 5

- Recording without pacing (1 d)
- Rapid atrial pacing (6 d, 10 Hz)

5-10 weeks

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Results
RVNA, LVNA and bipolar left atrial electrogram in sinus rhythm

RVNA associated with SB and pause

LVNA associated with SB and pause

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
RVNA, LVNA, IVC-IAGPNA during sustained AF

IVC-IAGPNA with LVNA (+)

IVC-IAGPNA with RVNA (+)

IVC-IAGPNA independent with VNA

RVNA activation after IVC-IAGPNA withdrawal

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
10-s integrated NA and ventricular rate: “L” shape relationship

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Slowing of VR associated with IVC-IAGPNA without RVNA or LVNA

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Relationship between RVNA, LVNA, IVC-IAGPNA and VR

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Circadian variation of linear correlation of LVNA, IVC-IAGPNA

(Park HW et al. Circ Arrhythm Electrophysiol 2012 In press)
Immunocytochemical staining of the cervical vagus nerve

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Conclusions

- IVC-IAGPNA and LVNA, but not RVNA, is associated with a reduction of VR to <100 bpm during AF in ambulatory dogs.

- It is possible that IVC-IAGP relays LVNA to atrioventricular node, resulting in VR reduction during sustained AF.

Park HW et al. Circ Arrhythm Electrophysiol 2012 In press
Chronic Electrical Neuronal Stimulation Increases Cardiac Parasympathetic Tone by Eliciting Neurotrophic Effects

Continuous Low-Level Vagus Nerve Stimulation Reduces Stellate Ganglion Nerve Activity and Paroxysmal Atrial Tachyarrhythmias in Ambulatory Canines

Chronic Atrioventricular Nodal Vagal Stimulation
First Evidence for Long-Term Ventricular Rate Control in Canine Atrial Fibrillation Model

- Long-term ventricular rate slowing during AF can be achieved by implantation of a nerve stimulator attached to the epicardial AVN fat pad. This novel concept is an attractive alternative to other methods of rate control and may be applicable in a selected group of patients.

Atrioventricular (AV) node vagal stimulation by transvenous permanent lead implantation to modulate AV node function: safety and feasibility in humans

- Selective placement of the atrial lead yields electrical characteristics suitable for permanent pacing and enables VR to be significantly reduced under HFS.

Vagal tone augmentation to the atrioventricular node in humans: Efficacy and safety of burst endocardial stimulation

- Endocordial right atrial burst AVNS reduces ventricular rate during AF.
- Burst AVNS delivered during SR in the effective atrial refractory period allows optimization of lead positioning for AVNS

Therapeutic Intervention of Autonomic Nervous System

- Reduce incidence of arrhythmia
- Modulation of contribution of each nerve activity to arrhythmogenesis
- Device able to modify autonomic nerve activity by feedback