Syncope

A Diagnostic and Treatment Strategy

Kevin McGrody MD, FACC

November 5, 2015
Syncope Presentation Overview

I. Prevalence & Impact
II. Etiology
III. Diagnosis & Evaluation
IV. Treatment
Prevalence & Impact

More than 1 million patients in the U.S.¹

More than 500,000 new patients per year¹

1-6% of admissions²,³,⁴

3% of emergency room visits per year³

¹ National Disease and Therapeutic Index on Syncope and Collapse, ICD-9-CM 780.2, IMS America, 1997
## Prevalence & Impact

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals &lt;18 yrs</td>
<td>15%</td>
</tr>
<tr>
<td>Military Population 17-46 yrs</td>
<td>20-25%</td>
</tr>
<tr>
<td>Individuals 40-59 yrs*</td>
<td>16-19%</td>
</tr>
<tr>
<td>Individuals &gt;70 yrs*</td>
<td>23%</td>
</tr>
</tbody>
</table>

*during a 10-year period

<table>
<thead>
<tr>
<th>Cause</th>
<th>Prevalence (Mean) %</th>
<th>Prevalence (Range) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflex-mediated:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Vasovagal</td>
<td>18</td>
<td>8-37</td>
</tr>
<tr>
<td>- Situational</td>
<td>5</td>
<td>1-8</td>
</tr>
<tr>
<td>Carotid Sinus</td>
<td>1</td>
<td>0-4</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>8</td>
<td>4-10</td>
</tr>
<tr>
<td>Medications</td>
<td>3</td>
<td>1-7</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>2</td>
<td>1-7</td>
</tr>
<tr>
<td>Neurological</td>
<td>10</td>
<td>3-32</td>
</tr>
<tr>
<td>Organic Heart Disease</td>
<td>4</td>
<td>1-8</td>
</tr>
<tr>
<td>Cardiac Arrhythmias</td>
<td>14</td>
<td>4-38</td>
</tr>
<tr>
<td>Unknown</td>
<td>34</td>
<td>13-41</td>
</tr>
</tbody>
</table>

Etiology

Bariatric surgery
- As bariatric surgery becomes an increasingly popular treatment for obesity, we have seen an increasing number of patients present after bariatric surgery with new-onset syncope, near-syncope, and lightheadedness.
- Several case series have shown increased symptoms after significant weight loss (mean 55 kg loss)

New-onset orthostatic intolerance following bariatric surgery.
Billakanty SR, Kligman MD, Kanjwal YM, Kosinski DJ, Maly GT, Karabin B, Grubb BP.
Primary Evaluation: Determine whether the patient is at increased risk of death

Identify risk of:
- Underlying structural heart disease
- Myocardial ischemia
- Wolff-Parkinson-White Syndrome
- Genetic disease such as the LQTS, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, ARVD

If none of the above risk then goal is to identify cause and improve quality of life
Diagnosis & Evaluation

Detailed History & Physical
- Document details of events
- Assess frequency, severity
- Obtain careful family history

Heart disease present?
- Physical exam
- ECG: long QT, WPW, conduction system disease
- Echo: LV function, valve status, HOCM

Follow a diagnostic plan...
## Diagnosis & Evaluation

<table>
<thead>
<tr>
<th>Test/Procedure</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(based on mean time to diagnosis of 5.1 months)</strong></td>
<td></td>
</tr>
<tr>
<td>History and Physical (including carotid sinus massage)</td>
<td>49-85% 1, 2</td>
</tr>
<tr>
<td>ECG</td>
<td>2-11% 2</td>
</tr>
<tr>
<td>Electrophysiology Study without SHD*</td>
<td>11% 3</td>
</tr>
<tr>
<td>Electrophysiology Study with SHD</td>
<td>49% 3</td>
</tr>
<tr>
<td>Tilt Table Test (without SHD)</td>
<td>11-87% 4, 5</td>
</tr>
<tr>
<td>Ambulatory ECG Monitors:</td>
<td></td>
</tr>
<tr>
<td>Holter</td>
<td>2% 7</td>
</tr>
<tr>
<td>External Loop Recorder (2-3 weeks duration)</td>
<td>20% 7</td>
</tr>
<tr>
<td>Insertable Loop Recorder (up to 14 months duration)</td>
<td>65-88% 6, 7</td>
</tr>
<tr>
<td>Neurological † (Head CT Scan, Carotid Doppler)</td>
<td>0-4% 4,5,8,9,10</td>
</tr>
</tbody>
</table>

5 Kapoor, *JAMA*, 1992  
6 Krahn, *Circulation*, 1995  

* Structural Heart Disease  
† MRI not studied
Diagnosis & Evaluation

12 Lead ECG
- Normal or Abnormal?
- Acute MI
- Severe Sinus Bradycardia/pause
- AV Block
- Tachyarrhythmia (SVT, VT)
- Preexcitation (WPW), Long QT, Brugada, ARVD

ECHO
- Valvular heart disease
- Pulmonary embolism pulmonary hypertension
- HOCM
- Decreased LV function
Diagnosis & Evaluation

Ischemia evaluation

- If history and physical suggest coronary artery disease then ischemic work up would be reasonable
- Exercise testing with echocardiographic imaging to determine exercise related arrhythmia’s and underlying heart disease
Diagnosis & Evaluation

Head-up Tilt Test
- Unmasks VVS susceptibility
- Reproduces symptoms
- Patient learns VVS warning symptoms
- Physician is better able to give prognostic / treatment advice
Diagnosis & Evaluation

Patient history and physical exam

Tilt table test
(ACC Consensus Protocol)
- Overnight fast
- ECG
- Blood pressure
- Supine and upright
- Tilt to 70 degrees 20 min
- SL NTG or isoproterenol
- Re-tilt 15 min

DG Benditt, Tilt Table Testing, 1996.
Diagnosis & Evaluation

Conventional EP Testing in Syncope

- Limited utility in syncope evaluation
- Most useful in patients with structural heart disease
  - Heart disease........50-80%
  - No Heart disease...18-50%
- Relatively ineffective for assessing bradyarrhythmias
- Essentially we are looking for ventricular arrhythmias and whether the patient would need an ICD

Diagnosis & Evaluation

Long term ECG monitoring

- Holter useful if everyday recurrent episodes
- Event monitors for more infrequent episodes but limited by successfully acquiring event and transmitting data
- Implantable loop recorder
  - Minimal procedure
  - Up to 2 yr monitor time
  - Can be triggered as well as set for automatic recording
Treatment

Recognize life threatening causes of syncope
- Structural heart disease
  - Corrective surgery (valvular)
  - Physical limitations (HOCM)
- Predisposition to malignant fatal arrhythmia
  - Antiarrhythmic therapy
  - Device therapy
- Ischemic heart disease and revascularization
Treatment

Education
- symptom recognition
- reassurance
- situation avoidance

Tilt-Training
- prescribed upright posture

Pharmacologic Agents
- salt/volume management
- beta-adrenergic blockers
- SSRIs
- vasoconstrictors (e.g., midodrine)

Cardiac Pacemakers
VVS: Tilt-Training

- Objectives
  - Enhance Orthostatic Tolerance
  - Diminish Excessive Autonomic Reflex Activity
  - Reduce Syncope Susceptibility / Recurrences

- Technique
  - Prescribed Periods of Upright Posture
  - Progressive Increased Duration
Tilt-Training: Clinical Outcomes

42 HUT positive (21±13 min) VVS patients

Home training: two 30 minute sessions daily

Outcomes

- 41/42 pts --->45 min asymptomatic HUT
- Clinical follow-up: 15.1±7.8 mos
- 36 pts syncope free
- 4 pts: presyncope
- 1 pt: syncope recurrences
Treatment

Pharmacologic Rx

- Salt /Volume
  - Salt tablets, ‘sport’ drinks, fludrocortisone. Uncontrolled trials have shown effectiveness at reducing recurrent syncope
- Beta-adrenergic blockers (? diminish activation of C-fibers)
  - 5 of 7 controlled trials no significant benefit,
  - POST Trial\(^1\) RCT of metoprolol vs placebo in 208 pts. At 1 yr no difference in syncope free periods between groups
- Disopyramide, Enalapril, Theophylline, Ephedrine: No controlled trials

1 Sheldon R. POST Trial Late Breaking Clinical Trial HRS 2004
Pharmacologic Rx

- SSRI
  - 68 pt with positive HUT without success from other agents
  - Randomized to paroxetine 20mg or placebo for one month then repeat HUT
  - Negative HUT: paroxetine 61.8% vs placebo 38.2% p<0.0001
  - Follow up after 25 months: paroxetine 17.6% syncope vs placebo 52.9% p<0.0001
  - Concluded that paroxetine improved symptoms of VVS

Di Girolamo et al JACC 1999;33:1227-30
## Treatment

### Selective serotonin reuptake inhibitors: randomized placebo-controlled trials

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Drug</th>
<th>Follow-up period</th>
<th>Endpoint</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theodorakis et al[63], 2006</td>
<td>96</td>
<td>Fluoxetine</td>
<td>6 mo</td>
<td>Time to vasovagal episode</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Well-being</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Syncope episodes</td>
<td>NS</td>
</tr>
<tr>
<td>Di Girolamo et al[62], 1999</td>
<td>68</td>
<td>Paroxetine</td>
<td>6 mo</td>
<td>TT</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Syncope recurrence</td>
<td>0.001</td>
</tr>
</tbody>
</table>

TT: Head-up tilt table test; NS: Not significant.

Theodorakis et al  Europace. 2006;8:193–198
Di Girolamo et al JACC 1999;33:1227-30
Pharmacologic Rx

- Vasoconstrictors (e.g., midodrine)
- Several small RCT showing more symptom free days and better quality of life\textsuperscript{1,2,3}

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Follow-up period</th>
<th>Endpoint</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ward et al\textsuperscript{[57]}, 1998</td>
<td>16</td>
<td>1 mo</td>
<td>TT</td>
<td>0.01</td>
</tr>
<tr>
<td>Perez-Lugones et al\textsuperscript{[58]}, 2001</td>
<td>61</td>
<td>6 mo</td>
<td>Syncope recurrence</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Kaufmann et al\textsuperscript{[59]}, 2002</td>
<td>12</td>
<td>1 wk</td>
<td>TT</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Qingyou et al\textsuperscript{[60]}, 2006</td>
<td>26</td>
<td>42 mo</td>
<td>TT</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

TT: Head-up tilt table test.

1 Ward CR et al Heart 1998;79:45-9
Midodrine for Neurocardiogenic Syncope

Treatment

Midodrine
Fluid

Symptom – Free Interval

p < 0.001

Months

Treatment

Pacing for VVS
- VVS with +HUT and cardioinhibitory response a Class IIb indication

Clinical studies demonstrated benefits of pacing in select VVS patients:
- VPS I
- VPS II –Phase I
- VASIS
- SYDIT

### Treatment

**VPS-I Vasovagal Pacemaker Study I**
- 54 patients randomized, prospective, single center
  - 27 DDD pacemaker with rate drop response (RDR)
  - 27 no pacemaker
- Outcome:

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>PACEMAKER (n= 27)</th>
<th>CONTROL (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients w/syncopal recurrence</td>
<td>6 (22%)</td>
<td>19 (70%)</td>
</tr>
<tr>
<td>Mean time to first recurrence (days)</td>
<td>112</td>
<td>54</td>
</tr>
<tr>
<td>Relative risk reduction of syncope*</td>
<td>85.4%</td>
<td>-</td>
</tr>
</tbody>
</table>

VPS-II: Phase I Vasovagal Pacemaker Study-II

Study Design:
- 100 patients, randomized, prospective, multicenter
- 50 DDD pacemaker with rate drop response (RDR)
- 50 ODO pacemaker (inactive mode)

Outcome:

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>DDD Pacemaker (n= 50)</th>
<th>ODO Pacemaker (n= 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients w/syncopal recurrence</td>
<td>16 (32%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Relative Risk Reduction*</td>
<td>28.7%</td>
<td>-</td>
</tr>
</tbody>
</table>

*P=0.153

Treatment

VPS-II: Phase I
Vasovagal Pacemaker Study-II

P = 0.153 (one-sided)

Number at Risk

VASIS Vasovagal Syncope International Study

Study Design:

- 42 patients, randomized, prospective, multicenter
  - 19 DDI pacemaker (80 bpm) with rate hysteresis (45 bpm)
  - 23 no pacemaker
- Outcome:

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>Pacemaker (n=19)</th>
<th>No Pacemaker (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients w-syncopal recurrence</td>
<td>1 (5%)</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>Median time to first recurrence (months)*</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>

*P= 0.0006
Treatment

VASIS
Vasovagal Syncope International Study

Years
% syncope-free


Medicine of the Highest Order
SYDIT Syncope Diagnosis and Treatment Study

Study Design:
• 93 patients randomized, prospective, multicenter
  • 46 DDD pacemaker with rate drop response (RDR)
  • 47 Atenolol 100 MG/D

Outcome:

<table>
<thead>
<tr>
<th>RESULTS</th>
<th>PACED (n= 46)</th>
<th>DRUG (n= 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients w/ syncopal recurrence*</td>
<td>2 (4%)</td>
<td>12 (25%)</td>
</tr>
<tr>
<td>Median time to first recurrence (days)</td>
<td>390</td>
<td>135</td>
</tr>
</tbody>
</table>

SYDIT Syncope Diagnosis and Treatment Study

% of syncope free pts

Time (days)

0 10 20 30 40 50 60 70 80 90 100

P = 0.0032

Treatment

drug pacemaker
VVS Pacing Trials Conclusions

• DDD pacing with rate drop response reduces the risk of syncope in patients with recurrent, refractory, highly-symptomatic, cardioinhibitory vasovagal syncope

• In other words, patients with symptomatic bradycardia need a pacemaker
Syncope is a common clinical problem often debilitating and recurrent.

Initial evaluation should quickly determine if the patient has a high risk of death.

It is often difficult to treat but effective patient education and persistent appropriate medical or device therapy can be effective in diminishing the impact on our patients' lives.
Medicine of the Highest Order