Syncope: Evaluation and Evolution

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Syncope – What’s New?

What’s Trending?

- Specialized Treatment Centers
- Expedited REVEAL/ILR implantation “LINQ”
- Genetic basis for Vasovagal Syncope
- Vasovagal Syncope Prophylactic Medication Clinical Trials
- Evolution Of Pacemaker Therapy for Vasovagal Syncope
- Early Repolarization – Not always benign
- New Entities “Paroxysmal AV Block” and “Sudden Syncope with Normal Heart”
- What’s new in syncope at Cleveland Clinic?
- Obamacare!
Syncope - What’s New?
Affordable Health Care Act - Healthcare Evolution

• Perfect Storm of limited resources, declining reimbursement but greater access for the syncope patient

• PCPs will likely be on the frontline

• Declining Reimbursement ICD-9-CM code 780.2

• Fear of Limiting Specialty and Subspecialty access

• Tighter regulation on testing, e.g. Tilts not covered by many insurance plans

• Population continues to age, syncope incidence will likely increase

• Need for streamlined approach

• Costs are skyrocketing “Every test for every patient” will bankrupt the medical system e.g. Evolving and expanding indications for ICD for primary prevention
“…cardiac syncope can be a harbinger of sudden death.”

- Framingham study
  Survival with and without syncope
- 6-month mortality rate of greater than 10%
- Cardiac syncope doubled the risk of death

Syncope – Multiple Layers of Risk

• Mortality versus morbidity
• Long term risk versus short term
• Risk of Sudden death due to underlying SHD
• Risk of injury due to syncope eg syncope while on coumadin, syncope while driving, high risk occupation
• QOL – fear, anxiety, disability from syncope
Risk Considerations

• National and International guidelines not specific on who should see the patient

• Emphasize need for streamlined algorithm or “Care Path” Future incorporation into EHR

• Quality of Life concerns – driving occupation, safety, fear. Even a single episode of syncope can have a major life impact

• Recalcitrant/recurrent cases may require Tertiary care center/specialized syncope centers with multidiscipline approach eg, internists, neurologists, cardiologists, Electrophysiologists, gerontologists
Guidelines for the diagnosis and management of syncope (version 2009)

The Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC)

Developed in collaboration with, European Heart Rhythm Association (EHRA)¹, Heart Failure Association (HFA)², and Heart Rhythm Society (HRS)³

Endorsed by the following societies, European Society of Emergency Medicine (EuSEM)⁴, European Federation of Internal Medicine (EFIM)⁵, European Union Geriatric Medicine Society (EUGMS)⁶, American Geriatrics Society (AGS), European Neurological Society (ENS)⁷, European Federation of Autonomic Societies (EFAS)⁸, American Autonomic Society (AAS)⁹

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The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines
Syncope - Epidemiology

• Up to 60% of the population may have syncope in their lifetime.

• 500,000 new patients per year

• Many people with syncope don’t seek medical attention until it recurs, estimated to be almost 50%.

• Many patients forego ED and present to PCP

• 1-3% of ED visits

• 40% of ED patients are admitted, average LOS 5.5 days

• Staggering Health Care Cost - $2.4 Billion annually

• Syncope most common in flight emergency
What’s new in Syncope – Syncope Centers

• Specialized multi-discipline centers for rapid evaluation and triage of patient’s with syncope

• Fits and Faints, Falls, Fractures

• Initial contact through emergency department

• Rapid access to syncope specialists EEG cardiologists, internists, electrophysiologists

• Rapid risk assessment, and identification of high risk patients requiring in-hospital evaluation and treatment, such as pacemakers, defibrillators, EP studies, cardiac cath etc.
Utah/Wisconsin Falls Fainting Clinic

**Faint Algorithm**

1. Faint Initial Assessment
   - H&P exam
   - Orthostatic testing
   - ECG
   - Echocardiogram
   - Laboratory tests

2. In-hospital evaluation
   - Admission criteria?
     - YES
     - NO

3. Treatment
   - Diagnosis certain?
     - YES
     - NO

4. Uncertain Faint Evaluation
   - Cardiac syncope likely?
     - Cardiac tests & monitoring
   - Cardiac syncope unlikely: recurrent or severe symptoms?
     - Reflex tests & monitoring
   - Cardiac syncope unlikely: single/rare and mild symptoms?
     - Reflex tests
   - Non-syncopal faint likely?
     - Neurologic/Psychologic evaluation

Hamdan PACE 2013
Syncope - Definition

Transient Loss of Consciousness, loss of postural muscle tone due to Pan-Cerebral Hypoperfusion with complete recovery without Focal Neurologic Deficit

Excludes Seizures, TIA/ CVA, Metabolic etiologies, Psychogenic, Trauma, Sleep Disorders, Intoxication, Hypoxemia, Migraines, Hyperventilation

Part of the spectrum of "TLOC" - Transient Loss of Consciousness
Syncope – Epidemiology
Emergency Department

• 45% Males

• Bad prognostic sign - 0.7% die within 7-30 days, 10% die within a year

• Severe nonfatal outcomes, including injury from syncope recurrence, major intervention, new serious diagnosis - 8% while in ED, 5% in next 7-30 days
• Previously very heterogeneous in their approach With divergent tests such as chest CT to rule out dissection or pulmonary emboli

• Extensive laboratory, cerebrovascular imaging, cards and neuro consultations, MRIs

• Admission was seemingly recommended haphazardly

• Classic neurally mediated or vasovagal syncope were eventually discharged in recommended followup with PCP or occasionally cardiology
<table>
<thead>
<tr>
<th>Study</th>
<th>Risk factors</th>
<th>Score</th>
<th>Endpoints</th>
<th>Results (validation cohort)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Francisco Syncope</td>
<td>Abnormal ECG, Congestive heart failure, Shortness of breath, Haematocrit &lt;30%</td>
<td>No risk = 0 item</td>
<td>Serious events at 7 days</td>
<td>98% sensitive and 56% specific</td>
</tr>
<tr>
<td>Rule</td>
<td>Systolic blood pressure &lt;90 mmHg</td>
<td>Risk ≥ 1 item</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al.</td>
<td>Abnormal ECG, History of ventricular arrhythmia, History of congestive heart failure, Age &gt;45 years</td>
<td>0 to 4 (1 point each item)</td>
<td>1-year severe arrhythmias or arrhythmic death</td>
<td>0% score 0</td>
</tr>
<tr>
<td>OESIL score</td>
<td>Abnormal ECG, History of cardiovascular disease, Lack of prodrome, Age &gt;65 years</td>
<td>0 to 4 (1 point each item)</td>
<td>1-year total mortality</td>
<td>0.6% score 1</td>
</tr>
<tr>
<td>EGSYS score</td>
<td>Palpitations before syncope (+4), Abnormal ECG and/or heart disease (+3), Syncope during effort (+3), Syncope while supine (+2), Autonomic prodrome a (-1), Predisposing and/or precipitating factors b (-1)</td>
<td>Sum of + and − points</td>
<td>2-year total mortality</td>
<td>2% score &lt;3</td>
</tr>
</tbody>
</table>

This table shows several different studies that have analysed the impact of different clinical data on the follow-up of patients presenting with syncope. Overall, the presence of abnormal ECG, increased age, or data suggestive of heart disease imply a worse prognosis at 1–2 year follow-up.

aNausea/vomiting
bWarm-crowded place/ prolonged orthostasis/fear—pain—emotion.
ECG = electrocardiogram
Prognosis Among Healthy Individuals Discharged With a Primary Diagnosis of Syncope

- 37,017 patients seen in Denmark ED for new syncope without apparent heart disease or diagnosis
- Compared to non syncope controls
- Followed for death, recurrent syncope, PPM, ICD or stroke
- Syncope had double the mortality during follow up
- 25 to 75 y/o had significantly higher mortality and risk of cardiovascular event
- Speculation that syncope may be frequent cause of fatal accidents, MVAs,

“Low Risk is Not No Risk”
Ruwald JACC 2013
Outcomes of Medical Emergencies on Commercial Airline Flights


RESULTS

There were 11,920 in-flight medical emergencies resulting in calls to the center (1 medical emergency per 604 flights). The most common problems were syncope or presyncope (37.4% of cases), respiratory symptoms (12.1%), and nausea or vomiting (9.5%). Physician passengers provided medical assistance in 48.1% of in-flight medical emergencies, and aircraft diversion occurred in 7.3%. Of 10,914 patients for whom postflight follow-up data were available, 25.8% were transported to a hospital by emergency-medical-service personnel, 8.6% were admitted, and 0.3% died. The most common triggers for admission were possible stroke (odds ratio, 3.36; 95% confidence interval [CI], 1.88 to 6.03), respiratory symptoms (odds ratio, 2.13; 95% CI, 1.48 to 3.06), and cardiac symptoms (odds ratio, 1.95; 95% CI, 1.37 to 2.77).
Syncope: Etiology

Neurally-Mediated
1. Vasovagal
   • Carotid Sinus
   • Situational
     ➢ Cough
     ➢ Post-micturition
   24%

Orthostatic
2. Drug Induced
   • ANS Failure
     ➢ Primary
     ➢ Secondary
   11%

Cardiac Arrhythmia
3. Brady
   • Sick sinus
   • AV block
   • Tachy
     ➢ VT
     ➢ SVT
   • Long QT Syndrome
   14%

Structural Cardio-Pulmonary
4. Aortic Stenosis
   • HOCM
   • Pulmonary Hypertension
   4%

Non-Cardiovascular
5. Psychogenic
   • Metabolic
     e.g. hyper-ventilation
   • Neurological
   12%

Unknown Cause = 34%
Causes of Syncope

- Cardiac
- Arrhythmic
  - Nonarrhythmic

- Non-cardiac
Bad Things are Relatively Rare but We always Worry about them!
Potentially Fatal Causes for Syncope

- HOCM
- Wolff-Parkinson –White
- Myocardial Ischemia/Infarction
- Pulmonary Embolus
- Long QT Syndrome
- Brugada Syndrome
- Arrhythmogenic RV dysplasia
- Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)
- Aortic Stenosis
- Dissection
- Stroke/TIA/ Cerebral Hemorrhage
## Causes of Syncope by Age

<table>
<thead>
<tr>
<th>Younger Patient</th>
<th>Older Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vasovagal</td>
<td>• Cardiac**</td>
</tr>
<tr>
<td>• Situational</td>
<td>— Mechanical</td>
</tr>
<tr>
<td>• Psychiatric</td>
<td>— Arrhythmic</td>
</tr>
<tr>
<td>• Long QT*</td>
<td>• Orthostatic hypotension</td>
</tr>
<tr>
<td>• Brugada syndrome*</td>
<td>• Drug-induced</td>
</tr>
<tr>
<td>• WPW syndrome*</td>
<td>• Neurally mediated</td>
</tr>
<tr>
<td>• RV dysplasia*</td>
<td>• Multifactorial</td>
</tr>
<tr>
<td>• Hypertrophic cardiomyopathy*</td>
<td></td>
</tr>
<tr>
<td>• Catecholaminergic VT</td>
<td></td>
</tr>
<tr>
<td>• Other genetic syndromes</td>
<td></td>
</tr>
</tbody>
</table>

*Rare, not benign

**Not benign

Underlined: benign

Syncope in the Elderly

- Multifactorial
- Medications - vasodilators, diuretics, BB’s
- SSS, CSM
- Unexplained falls - Retrograde amnesia - “Fits Falls Fractures Clinics”
- Impaired autonomic reflexes - Post Prandial drop in BP due to splanchnic sequestration - “Pizza Tilt”
Approach to Syncope

“Spell”
Unexplained altered or loss of consciousness

History
Physical (Cardiac-Neurologic)
ECG

Probable Clinical Diagnosis

1 Cardiac
Arrhythmias
Obstructive

Cardiac Risk Factors?
- LV dysfunction
- Abnormal ECG
- Older Patients
- ASHD

Cardiac Cath
Echocardiogram

Extended ECG Monitoring
Return to 1, 2 or 3

Cardiac Electrophysiology Study

Presumptive Diagnosis with Clinical Correlation

Definitive Diagnosis
Appropriate Therapy

2 Neuro-Regulatory

Head-up tilt
Hemodynamics
Blood Volume
Autonomic Testing
Carotid Sinus Massage

3 Neurologic Consultation

EEG
CT scan
Other tests as appropriate

Return to 1 or 2

Return to 1 or 2
Figure Legend:
The Diagnostic Algorithm of a Patient Presenting With TLOC of Suspected Syncopal Nature
For explanation, see text. ECG = electrocardiogram; TLOC = transient loss of consciousness.
Syncope – Risk Stratification
Two immediate questions to consider for First Responder

• Can the syncope be a warning sign for future sudden cardiac death?

• What is the risk of recurrence of the syncope and severe physical injury?
Syncope

History!

History!!

HISTORY!!!
Syncope – Initial Assessment

- History/ Physical
- Orthostatics – standing BP/HR immediate, 1 minute and 3 minutes (or longer for covert OH)
- EKG
- Echo +/- Stress
- Lab, esp CBC, Lytes
- Holter/ Ambulatory monitoring
- Tilt if suggestive of VVS, POTS, Dysautonomia
  - Admit, Reassure or Refer

- Cardiology/EPS Referral – Cath, EP study, ILR
History

- Position/posture
- Vision/Smell/Sound
- Frequency
- Duration
- Pain, Headache
- Vagal symptoms – Diaphoresis, Nausea, Emesis, Pallor, Cyanosis
- Prodrome/warning? Angor Animi
- Sequelae - Confusion? Post ictal? Instant Recovery?
- Injuries
- Witnesses - Movement of head, trunk, extremities? Sustained or Brief?
- Tongue biting, incontinence
Cough/Tussive Syncope

- Cardiopulmonary Baroreflex with vasodepression, occasional pauses, bradycardia, AV block, ? Elevation of CSF pressure
- Search for ENT/pulmonary cause
- Treatment: cough suppression, aerosol Lidocaine
High Risk /Malignant Syncope/Red Flags

• CHF, CAD, DM, Cardiac Risk Factors
• Abnormal EKG
• Injuries
• No apparent noxious stimuli/precipitating event
• No warning/ Minimal Prodrome
• Syncope while Driving
• Palpitations prior or after (Vagal Atrial Fibrillation, Arrhythmias)
• Chest pain before or after, Dyspnea
• Syncope with exercise, especially during (syncope in recovery could be autonomic)
• Medical Dx ie Sarcoid, Lymes, Dystrophies
• High Risk occupation
Syncope – Low risk

• Previous Multiple Syncopal events
• Normal EKG
• Normal Physical
• Normal Echo
• No history structural heart disease or arrhythmias
• Typical vagal symptoms
Syncope – Predicting Recurrence

• Of all comers 33% will have recurrence in 3 years

• Age over 40 but low risk – up to 20% recurrence at 2 years

• 3 previous life time syncope – 42% at 2 years

• High number of syncope episodes suggest reflex syncope

• Extreme number suggest Pseudosyncope
Syncope

**Value of History in Differentiation**

• 80 patients with syncope
  – 32 neurocardiogenic
  – 16 AV block
  – 32 ventricular tachycardia

• Age 58 + 17 years

• All underwent comprehensive questionnaire

*Calkins AJM 1995*
Syncope Due to AV Block or VT

- ≤ 2 episodes of syncope
- Male sex
- Warning ≤ 5 seconds
- Age >54 years

Calkins AJM 1995
Syncope Due to NCS and not due to VT/AV Block

• Prior to Syncope
  – Palpitations
  – Blurred vision
  – Nausea
  – Warmth
  – Diaphoresis
  – Lightheadedness

Calkins AJM 1995
Syncope Due to NCS and not Due to VT/AV Block

• Following Syncope
  – Nausea
  – Warmth
  – Diaphoresis
  – Fatigue
Syncope - Clues from the History

- Family History of SCD = LQTS, Brugadas, HCM, ARVD/C ? Drownings, ?MVAs
- Tongue biting, incontinence = Seizure
- Motion sickness, migraines, childhood fainting, athlete, hypervagotonia, early repolarization on EKG, Family Hx of fainting, phobic/pain fainting = Vasovagal
- Head turning = Carotid sinus syndrome
- Many episodes, vagal symptoms, prolonged warning, = Vasovagal “Status Vasovagalis”
- No prodrome, no symptoms post, Male sex, first episode over age 55 = AV block or VT
Orthostatic Hypotension

- Syncope in AM, with rapid standing, post prandial
- Systolic drop 20-30 mmHg, diastolic drop 10 mmHg or SBP < 90 although usually much more clinically
- Most common secondary causes – DM, Medications, Volume depletion
- Primary autonomic failure relatively rare and usually obvious - Parkinsons, cancer/paraneoplastic, Multi System atrophy (Shy – Dragger)
Deglutition/ Swallow Syncope
ARVD – Arrhythmogenic Right Ventricular Dysplasia

- RBBB/ epsilon waves, t - wave abnormality - “juvenile t wave pattern”
- Fatty - fibrous infiltration of right ventricle
- Characteristic findings of fatty infiltration on CT/MRI
- Syncope due to SMVT or PMVT
- Genetic testing
- ICD, AAD, RFA if syncope or SCD
Brugada’s Syndrome

- Channelopathy with VT/VF
- RBBB and ST segment elevation in anterior precordial leads
- Genetic testing – Familion
- Flecainide or Procainamide challenge
Trifascicular Block – RBBB, First degree AV block, LAHB
Syncope – EKG monitoring

• Holters – useless unless something happens

• Event recorders - continuous loop recorder

• Implantable
  – Reveal and Confirm - inplantable loop recorder
  – Pacemakers/ICDs with wireless transmission

• Ambulatory Wireless long term monitoring for diagnosis/prevention – MCOT (Mobile Cardiac Outpt Telemetry) continuous loop recorder using cellular networks, bluetooth e.g. Cardionet, Lifewatch

• Future devices will incorporate BP,O2 etc
Urgent - 2nd Degree AVB, Type 2, Dr. Moualla notified

Findings:
Urgent-Normal Sinus Rhythm with Ventricular Tachycardia 7 beats, Rate 145 bpm, Connie notified

Activities: None Indicated

Symptoms: None Indicated
Wireless Ambulatory ECG Monitors

- CardioNet, Lifewatch, others
- Automatic/Patient activated
- External 3 Lead/Portable Monitor Wireless Connection to Service
- GPS Capable, Altimeter
- Aimed at Low Risk Patient - Not in 911 business
  - Atrial fibrillation
  - SVT
  - SSS
  - Syncope of Undetermined Origin
  - Cryptogenic Stroke
  - Refractory Seizures
Ambulatory Monitoring - Summary

- Choose monitor likely to have highest yield.
- Pts with daily events, palpitations, syncope/near syncope, holters frequently are sufficient.
- Weekly or monthly events use wireless monitors
- Pts with rare events, consider referral for Implantable Loop recorders.
- Elderly, No prodrome or no warning, prolonged spells, solitary, Use wireless or implanted loop
- Valuable if symptoms but NSR, Sinus Tachycardia. Tells you what its not.
Reveal/Reveal Plus/ DX /XT - Medtronic Insertable Loop Recorder -ILR

- Records EKG – not electrogram
- Minimal Incision – Low Risk
- Appropriate Patient Selection –early utilization
  - Syncope in Normal Hearts
  - Fleeting Suspected SVT’s
  - Drug Refractory Seizures
  - Cryptogenic CVAs
- Inappropriate for High Risk Patients
  - Severe LV/Post MI
  - VT Suspected
  - Structural Heart Disease
Figure 1. Loop recording demonstrating sinus rhythm with an episode of artefact overlying it and correlating with the clinical event.
Syncope Strategies – Cost Comparisons

- Sixty Pts recurrent syncope, normal LV function.
- Randomized to Tilt, EPS (Conventional) versus Loop recorder.
- Crossover at one year if no diagnosis.
- 47% diagnosed with ILR, $2731 per Pt, $5852 per diagnosis
- 20% conventional approach, $1683 per Pt, $8414 per diagnosis
- Higher yield more cost effective with Loop recorder
Figure 2. Cost and diagnostic yield of the two treatment strategies. The results of the testing strategy are shown for all patients in the trial, including those who crossed over. The overall diagnostic yield of the two strategies was comparable, but the cost per diagnosis of the strategy of primary monitoring was significantly reduced by $2,016 (p = 0.002).
Medtronic Reveal LINQ
Pacemaker Therapy in Patients With Neureally Mediated Syncope and Documented Asystole

Third International Study on Syncope of Uncertain Etiology (ISSUE-3)

A Randomized Trial

Michele Brignole, MD; Carlo Menozzi, MD; Angel Moya, MD; Dietrich Andresen, MD; Jean Jacques Blanc, MD; Andrew D. Krah, MD; Wouter Wieling, MD; Xulio Beiras, MD; Jean Claude Deharo, MD; Vitantonio Russo, MD; Marco Tomaino, MD; Richard Sutton, DSc; on behalf of the International Study on Syncope of Uncertain Etiology 3 (ISSUE-3) Investigators
International Study of Syncope - Issue 3

- 511 patients with recurrent syncope suspected to be vasovagal
- All underwent Implantable loop recorder
- 89 patients had recurrent syncope with pauses
- 79 patients received Pacemaker implant if documented pauses > 3 seconds if symptomatic or > 6 sec pause if no symptoms
- Pacemaker programed on or off
- 57% recurrence with PPM off
- 25% recurrence with PPM on

Brignole  Circulation 2012
Limitations of ISSUE 3

- Variability of cardioinhibitory responses
- Only 10% were found to have pauses during study
- Doesn’t address the vasodepressor response
- Role of rate drop / What type? Hysteresis? CLS?
Non Ischemic Dilated Cardiomyopathy and Syncope

• Portends a high mortality
  —(45% at one year) regardless of cause

• EPS for SMVT - often unrevealing/non predictive

• No prospective studies of “Empiric ICD”

• Now Moot by Definite, SCD-Heft
Indications for EPS

- Prior MI
- LV Dysfunction/Cardiomyopathy Moot by Definite SCD-Heft
- Wide QRS – LBBB/RBBB, ?Brugadas
- Systemic Illness
  - Sarcoid
  - Lymes
- Prolonged PR, Mobitz 1
- “Complex” Ventricular Ectopy – NSVT
- SVT, Delta Wave
- Family HX of SCD
- Palpitations
- “Final Court of Appeals” Although EPS likely low yield in normal hearts
Neurally Mediated Syncope

- Vasovagal syncope
- Carotid sinus syncope
- Tussive syncope
- Glossopharyngeal neuralgia / deglutition syncope
- Pallid breath holding spells
- Aortic stenosis
- Hypertrophic obstruction cardiomyopathy
- Pacemaker syncope
- Syncope secondary to pulmonary hypertension
- Micturition syncope
- Mess trick – Fainting Lark
- Diving reflex
- Syncope during Atrial fibrillation, VT and SVT may have Neurally mediated contribution and component
Vasovagal Syncope

• Comprises significant proportion of unexplained syncope

• 60% of population are estimated to have at least one episode

• ANS perturbations - Sudden hypotension/bradycardia resulting in loss of consciousness

• Presumed trigger is augmented inotropic, chronotropic cardiac state

• Bezold Jarisch Reflex - sudden withdrawal of sympathetic/heightened or unopposed vagal

• Episodes may cluster, the disappear for long intervals
Vasovagal Syncope: Features

• Crumple to ground - injuries are rare
• May recur
• Slow recovery - "Vagal " for hours
• Myoclonic jerking "anoxic seizure", Convulsive Seizure
• Diming of vision, "grey out", Diaphoresis, nausea, pallor, warmth
• Hyperventilation - "shortness of breath"
• Yawning, weakness
• Palpitations, "chest pain"
• Fight or Flight
Genetic Basis for Vasovagal Syncope

- Frequently multiple members of same family are fainters
- ? Nature or Nurture/State or Trait? “All in the Family”
- Berkovic found autosomal dominant vasovagal susceptibility from loci on chromosome 15q26 (Neurology 2013)
- Uncertain what these genes code for? Protein? ion channels? Enzymes? Neurotransmitters? Cardiac, peripheral or CNS?
Vasovagal Syncope

• Benign/Situational
  – Emotional faint
  – Fear, pain - “The Paleolithic – Threat Hypothesis” Darwinian Fitness
  – Dentist, church, Restaurant, phlebotomy

• Malignant
  – No recognized stimulus
  – Little or no prodrome
  – Prolonged asystole
  – Injuries
  – Social impact – Loss of Occupation, Driving
Malignant Vasovagal Syncope
Situations which Provoke Vasovagal Syncope

• Fear, anxiety, “flight or fight”, pain, venipuncture
• Pregnancy, standing “at attention”
• Hypovolemia, anemia, hemorrhage
• Head-up tilt, lower body negative pressure
• “First dose phenomena”, nitrates
• Beta-blocker withdrawal
• Prolonged bed rest, prolonged head down tilt, microgravity
Tilt Table Test

• Traditional research tool for postural effects on BP and arrhythmias
• Control subjects with syncope were observed to faint
• Maximizes venous pooling
• Provokes vasovagal syncope in susceptible patients
Head Up Tilt: Indications

- Syncope of unknown origin
  - Suspected vasovagal

- Syncope with observed SA or AV dysfunction
  - Extrinsic sick sinus syndrome

- Seizures versus Syncope

- Pseudoseizure/Psychogenic Syncope
  - Arterial line, Transcranial Doppler, EEG

- PAF with Syncope
Asystole and Convulsive Syncope During Head-up Tilt

A. Onset of Vasovagal Syncope

B. Prolonged Asystole

C. After IV Atropine
Tilt Table Testing Indications

Emerging Indications

• POTS – Postural Orthostatic Tachycardia Syndrome, Dysautonomia
• Orthostatic Hypotension, Autonomic Insufficiency
• Idiopathic Vertigo, Dizziness, Lightheadness
• TIA’s
• Chronic Fatigue Syndrome, Fibromyalgia, Gulf war syndrome
• Sudden Infant Death Syndrome (SIDS), Pallid Breath Holding Spells
• Unexplained Falls

Not Warranted

Single episode in “classic” patient
Alternative specific cause demonstrated
Vasovagal Syncope

Tenets of Treatment

- Reassurance / Recognition / Avoidance
- Increase salt/ electrolyte fluids - 5-7 grams per day / florinef
- Physical Countermeasure Maneuvers (PCM) Supine position, Leg Crossing, Muscle tensing Circ 2002
- Coughing
- Jobst / physical therapy / Avoid deconditioning
- Serial tilt testing not predictive
- Tilt Table Training - Ector
# Recommendations: treatment of reflex syncope

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explanation of the diagnosis, provision of reassurance, and explanation of risk of recurrence are indicated in all patients</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Isometric PCMs are indicated in patients with prodrome</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Cardiac pacing should be considered in patients with dominant cardioinhibitory CSS</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Cardiac pacing should be considered in patients with frequent recurrent reflex syncope, age &gt;40 years, and documented spontaneous cardioinhibitory response during monitoring</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Midodrine may be indicated in patients with VVS refractory to lifestyle measures</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Tilt training may be useful for education of patients but long-term benefit depends on compliance</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Cardiac pacing may be indicated in patients with tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age &gt;40 after alternative therapy has failed</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>β-Adrenergic blocking drugs are not indicated</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

*Class of recommendation.

Level of evidence.

CSS = carotid sinus syndrome; PCM = physical isometric counterpressure manœuvre; VVS = vasovagal syncope.
## Vasovagal Syncope

### Medical Therapy

- **Fludrocortisone** - Mineralocorticoid
- **Disopyramide**
- **Serotonin reuptake inhibitors**
  - Sertraline, Fluoxetine
- **Anticholingerics**
  - Levsin, Transderm scopolamine, Robinul
- **Theophylline** - adenosine receptor blockade
- **Amphetamines, Ritalin**
- **Calcium channel blockers**
- **Epogen, DDAVP, Yohimbine, Mestinon - Grubb**

### International Goal for 2020

- Find a Proven Effective Therapy for Vasovagal Syncope
Vasovagal Syncope  Physical Counter pressure Measures/Maneuvres (PCM)

• Arm and leg tensing, isometrics applied at prodrome

• Immediate increase in venous return, reduction of venous pooling and possible autonomic effects

• Advise patient to get flat supine at earliest warning but ultimately be effective upright, even during tilt (tilt training effect?)

• Several studies have shown significant syncope recurrence reduction.
Prevention of Syncope Trial (POST): A Randomized, Placebo-Controlled Study of Metoprolol in the Prevention of Vasovagal Syncope
Robert Sheldon, Stuart Connolly, Sarah Rose, Thomas Klingenstein, Andrew Krahm, Carlos Morillo, Mario Talajic, Teresa Ku, Fennat Fouad-Tarazi, Debbie Ritchie and Mary-Lou Koshman

_Circulation_. 2006;113:1164-1170; originally published online February 27, 2006;
doi: 10.1161/CIRCULATIONAHA.105.535161
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539
Prevention of Syncope Trial (POST)

- Metoprolol versus Placebo in 208 patients with recurrent Vasovagal syncope
- Syncope recurred in 75 patients
- No difference in therapy
- Metoprolol not effective
- Beta blockers now class 3 (no benefit) with ACC and international guidelines
- Possible benefit in older patients, Patients >42 yo had reduction of syncope recurrences (Sheldon Circulation 2012)

Sheldon  Circulation 2006
Vasovagal Syncope – POST 2 Trial

- Randomized placebo control trial of Florinef in vasovagal syncope
- 211 patients with recurrent vasovagal syncope randomized to placebo vs florinef
- Endpoint was syncope recurrence (not number of episodes)
- Data still being analyzed, but there was no statistically significant syncope recurrence reduction but there was a trend
- Likely may have benefit shown in young, non hypertensive patients
- POST 4 - Randomized Trial of Midodrine
Recurrent Vasovagal Syncope - Pharmacologic Treatment

- Florinef if low Blood Volume
- Levsin for young, hypervagotonic pts
- Beta blockers if tilt suggests hyperadrenergic state, hyperkinetic circulation
- Midodrine if low grade orthostasis, CFS, FM
- SSRI esp if additional DXs
PRESS RELEASE
Feb 18, 2014, 4:53 p.m. EST

Chelsea Therapeutics Announces FDA Accelerated Approval of NORTHERA™ (Droxidopa) for the Treatment of Symptomatic NOH

First New Treatment Option for Symptomatic NOH in Nearly Two Decades First and Only FDA Approved Therapy to Demonstrate Symptomatic Benefit in Patients with NOH

CHARTER, N.C., Feb 18, 2014 (BUSINESS WIRE) -- Chelsea Therapeutics International, Ltd. today announced that the U.S. Food and Drug Administration (FDA) granted accelerated approval of NORTHERA(TM) (droxidopa) for the treatment of symptomatic neurogenic orthostatic hypotension (NOH). NORTHERA is the first and only therapy approved by the FDA which demonstrates symptomatic benefit in patients with NOH.

Pharmacy News

Droxidopa Approved for Neurogenic Orthostatic Hypotension

Kate Traynor

BETHELDA, MD 19 February 2014—Droxidopa, a synthetic amino acid precursor of norepinephrine, has been approved as oral therapy for the treatment of neurogenic orthostatic hypotension, FDA and Chelsea Therapeutics announced February 18.

The company expects the drug to be available during the second half of this year under the brand name Northera.

Labeling (PDF) for droxidopa states that it is indicated for the treatment of orthostatic dizziness, lightheadedness, or the sensation of impending fainting in adults with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure, dopamine β-hydroxylase deficiency, or non-diabetic autonomic neuropathy.
Droxidopa – (Northera)

- Norepinephrine Precursor converted to Norepi by sympathetic neurons
- Causes tremendous BP elevation, especially supine
- Approved by FDA in US Feb 18, 2014, anticipated availability late 2014
- Indications – severe persistent neurogenic OH from MSA, Parkinsons, PAF
- May improve cognitive impairment through central enhancement of Norepi
- Uncertain role for treatment of Reflex/Neurally Mediated Syncope
Syncope due to Idiopathic Paroxysmal AV Block

- 18 patient’s with recurrent syncope
- Normal heart
- Implantable loop recorders in most
- Spontaneous third degree/complete heart block without evidence of vagal stimulation
- Normal conduction system/Normal EKGs, normal PR and QRS/normal His-Purkinje
- Etiology? Intrinsic AV node disease or autonomic reflex
Syncope without Prodrome in Normal Heart and Normal EKG

- A new distinct syncope entity, not typical vasovagal syncope
- Sudden onset of syncope, no warning or vagal symptoms
- Patients were generally older and Syncope started at older age
- Decreased plasma adenosine levels
- Complex neurohumoral pathways
- May be related to idiopathic paroxysmal AV block and hence benefit from pacemakers
Natural History of Neurocardiogenic Syncope

**Spontaneous Resolution in Untreated Patients**

Recurrence - Free Probability

- $n = 54$
- Age = $48 \pm 12$ yrs
- Episodes = $10.2 \pm 7$
- Duration = $6.4 \pm 85$ yrs

Natale, AJC 1995
Pacemakers for Vasovagal Syncope

- Cardioinhibitory response confirmed by loop recorder
- “Highly” symptomatic, multiple episodes with injuries
- Drug failures
- Elderly – overlap with SSS, CSS
- Rate drop / hysteresis /CLS
- High risk occupations - Pilot / high steel / commerical driver

Elton John given pacemaker for heart irregularity

July 10, 1999
Web posted at: 8:51 AM EDT (1251 GMT)

LONDON (AP) -- Sir Elton John has had a pacemaker inserted to overcome what he called “a minor imbalance in my heart.”
Carotid Sinus Syncope

- Highest Incidence in Elderly
- Hypersensitive carotid sinus reflex with transient asystole or AV block and hypotension
- Episodes occur with head turning, shaving, adjusting tie, looking up, etc
- Treatment with PPM
- Testing with carotid sinus massage
- Amnesia of Event - “Fits, Falls, Faints and Fractures Clinic”
Patients with Syncope – Low Risk for death

• Remote episode without recurrence/ low risk patient
• Typical Benign Vasovagal episode known stimulus eg sight of blood, pain, prolonged standing, dentist, church
• Reassure – prognosis is excellent
• Minimal workup - Normal EKG+/- Echo
• Severe orthostatic hypotension at bedside, although may require multi discipline approach
Syncope – When to Admit for expedited evaluation?

• S. Francisco rule – CHF, Crit<30%, abnormal ECG, SOB, Systolic<90 “CHESS”

• EGYSYS, ROSE – Palps, syncope supine or during exercise, High BNP, Low O2, Q waves, occult blood

• Structural heart disease – CAD, DCM, CHF, MIs

• Family history of SCD, HOCM, Brugadas Syndrome, DCM

• Conduction/Repolarization Abnormalities - Trifascicular Block, LBBB, LQTS, Short QT syndrome, Early Repolarization

• Features – sudden LOC without prodrome, MVAs, possible SZs, Fractures, Head or bodily injuries, Chest pain or exercise induced
Syncope – Risk Stratification “Higher risk”
Possible indication for admission or expedited workup

• Malignant Features of the Syncope
• Abnormal Holter / EKG/ Murmurs
• Suspected /Confirmed Vasovagal but Recurrent
• Cardiac Risk Factors
• Concerning Family History
• Occupational concerns
• Recurrent Unexplained falls especially in elderly
Syncope Additional Considerations for expedited workup

• Patient Request
• Clearly Vasovagal but recurrent – Need for additional treatment such as ILR/ pacemaker
• Medico legal: risk of bad outcomes is small but not zero
• 30-50% of syncope remains unexplained; suspected vasovagal
• Driving – Guidelines are vague and inadequate
Syncope - What’s in the future?

- Fast track, guideline based syncope units
- Improved access
- Cost reduction
- Better outcomes
- Earlier utilization of Implantable loop recorders, ultimately with BP monitors
Syncope 2020: Five Grand Challenges

- Learn the cause and integrated physiology of vasovagal syncope by 2020.
- Develop at least 1 effective treatment of moderately frequent vasovagal syncope in patients without complications by 2020.
- Develop at least 1 effective treatment of vasovagal syncope in patients with confounding comorbidities such as hypertension by 2020.
- Reduce yearly health care spending on syncope by 25% while improving the diagnosis rate and patient satisfaction by 2020.
- Develop an individualized approach to most patients with syncope by 2020.

Sheldon Cardiology Clinic 2013