Syncope: Evaluation and Evolution

Fred Jaeger DO

Center for Syncope and Autonomic Disorders

Section of Electrophysiology, Department of Cardiovascular Medicine

Miller Heart and Vascular Institute

Cleveland Clinic

Syncope – What's New? What's Trending?

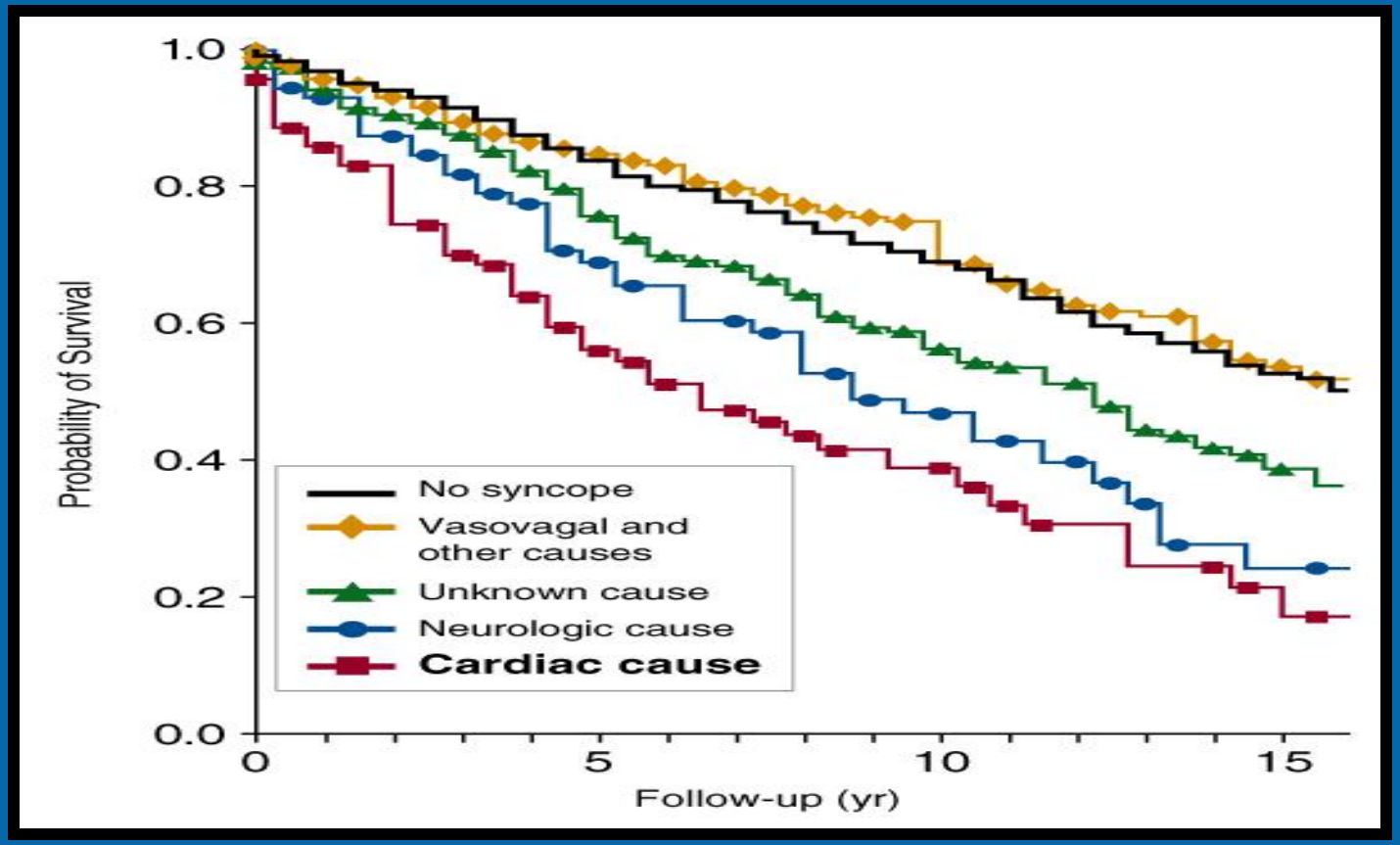
- Specialized Treatment Centers
- Expedited REVEAL/ILR implantation "LINQ"
- Genetic basis for Vasovagal Syncope
- Vasovagal Syncope Prophylactic Medication Clinical Trials
- Evolution Of Pacemaker Therapy for Vasovagal Syncope
- Early Repolarization – Not always benign
- New Entities "Paroxysmal AV 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 eg 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



Soteriades ES, et al. *NEJM* . 2002;347:878-885.

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

European Heart Journal (2009) 30, 2631–2671
doi:10.1093/eurheartj/ehp298

ESC GUIDELINES

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]

Authors/Task Force Members, Angel Moya (Chairperson) (Spain)*, Richard Sutton (Co-Chairperson) (UK)*, Fabrizio Ammirati (Italy), Jean-Jacques Blanc (France), Michele Brignole[1] (Italy), Johannes B. Dahm (Germany), Jean-Claude Deharo (France), Jacek Gajek (Poland), Knut Gjesdal[2] (Norway), Andrew Krahn[3] (Canada), Martial Massin (Belgium), Mauro Pepi (Italy), Thomas Pezawas (Austria), Ricardo Ruiz Granell (Spain), Francois Sarasin[4] (Switzerland), Andrea Ungar[6] (Italy), J. Gert van Dijk[7] (The Netherlands), Edmond P. Walma (The Netherlands), Wouter Wieling (The Netherlands)

External Contributors, Haruhiko Abe (Japan), David G. Benditt (USA), Wyatt W. Decker (USA), Blair P. Grubb (USA), Horacio Kaufmann[9] (USA), Carlos Morillo (Canada), Brian Olshansky (USA), Steve W. Parry (UK), Robert Sheldon (Canada), Win K. Shen (USA)

ESC Committee for Practice Guidelines (CPG), Alec Vahanian (Chairperson) (France), Angelo Auricchio (Switzerland), Jeroen Bax (The Netherlands), Claudio Ceconi (Italy), Veronica Dean (France), Gerasimos Filippatos (Greece), Christian Funck-Brentano (France), Richard Hobbs (UK), Peter Kearney (Ireland), Theresa McDonagh (UK), Keith McGregor (France), Bogdan A. Popescu (Romania), Zeljko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendera (Poland), Panos Vardas (Greece), Petr Widimsky (Czech Republic)

Document Reviewers, Angelo Auricchio (CPG Review Coordinator) (Switzerland), Esmeray Acarturk (Turkey), Felicita Andreotti (Italy), Riccardo Asteggiano (Italy), Urs Bauersfeld (Switzerland), Abdelouahab Bellou[4] (France), Athanase Benetos[6] (France), Johan Brandt (Sweden), Mina K. Chung[3] (USA), Pietro Cortelli[8] (Italy), Antoine Da Costa (France), Fabrice Extramiana (France), José Ferro[7] (Portugal), Bulent Gorenek (Turkey), Antti Hedman (Finland), Rafael Hirsch (Israel), Gabriela Kaliska (Slovak Republic), Rose Anne Kenny[6] (Ireland), Keld Per Kjeldsen (Denmark), Rachel Lampert[3] (USA), Henning Mølgard (Denmark), Rain Paju (Estonia), Aras Puodziukynas (Lithuania), Antonio Raviele (Italy), Pilar Roman[5] (Spain), Martin Scherer (Germany), Ronald Schondorf[9] (Canada), Rosa Sicari (Italy), Peter Vanbrabant[4] (Belgium), Christian Wolpert[1] (Germany), Jose Luis Zamorano (Spain)

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

Syncope - Epidemiology

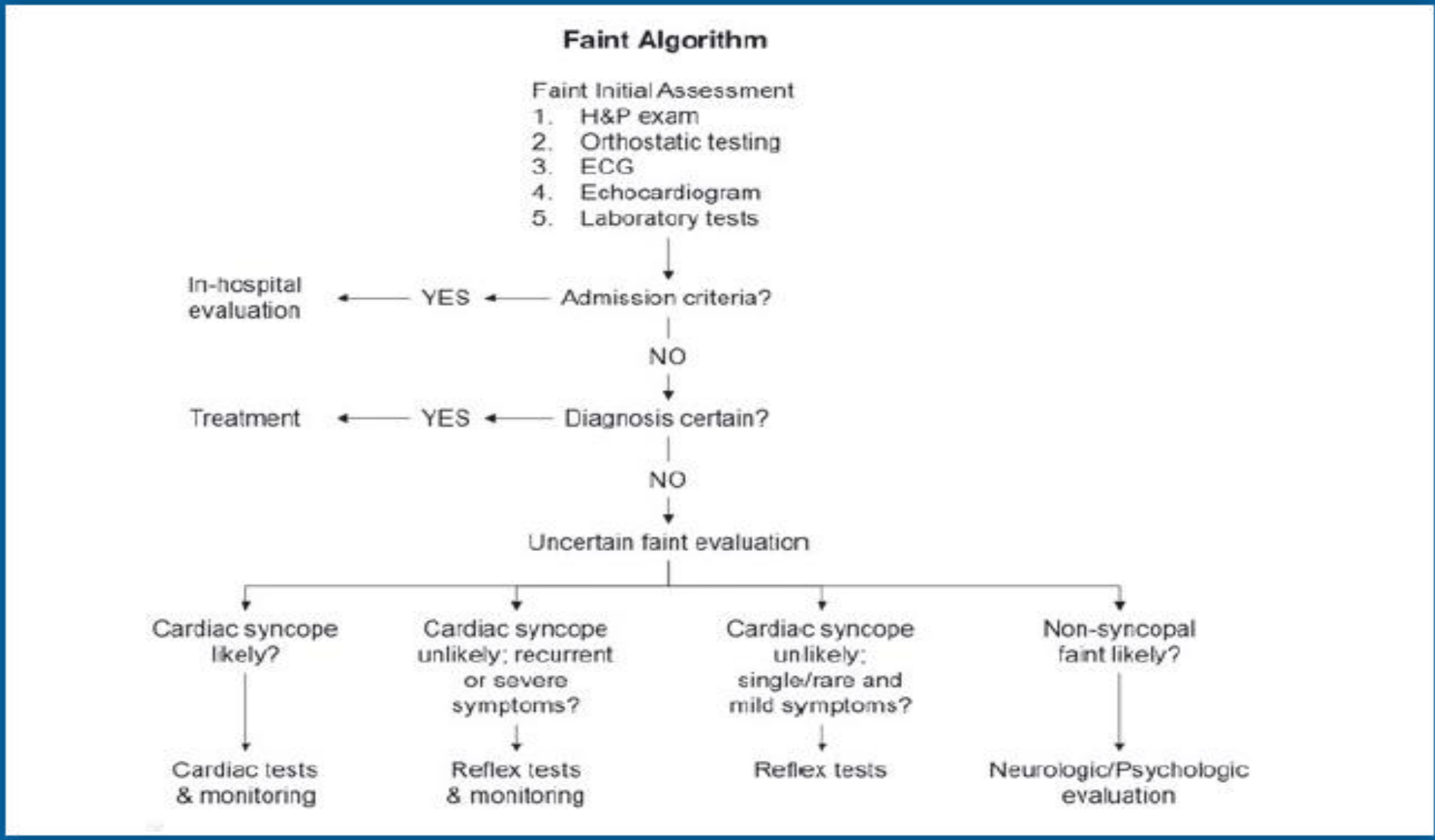
- Up to 60% of the population may have syncope in their lifetime.
- 500,000 new patients per year
- Many people with syncope don’t seek medical attention until it recurs, estimated to be almost 50%.
- Many patients forego ED and present to PCP
- 1-3% of ED visits
- 40% of ED patients are admitted, average 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 andtreatment, such as pacemakers, defibrillators, EP studies, cardiac cath etc.

Utah/Wisconsin Falls Fainting Clinic



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

Syncope – Evaluation in the Emergency Department

- 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 8 Risk stratification at initial evaluation in prospective population studies including a validation cohort

Study	Risk factors	Score	Endpoints	Results (validation cohort)
S. Francisco Syncope Rule[44]	-Abnormal ECG -Congestive heart failure -Shortness of breath -Haematocrit <30% -Systolic blood pressure <90 mmHg	No risk = 0 item Risk = ≥1 item	Serious events at 7 days	98% sensitive and 56% specific
Martin *et al.* [40]	-Abnormal ECG -History of ventricular arrhythmia -History of congestive heart failure -Age >45 years	0 to 4 (1 point each item)	1-year severe arrhythmias or arrhythmic death	0% score 0 5% score 1 16% score 2 27% score 3 or 4
OESIL score[41]	-Abnormal ECG -History of cardiovascular disease -Lack of prodrome -Age >65 years	0 to 4 (1 point each item)	1-year total mortality	0% score 0 0.6% score 1 14% score 2 29% score 3 53% score 4
EGSYS score[42]	-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)	Sum of + and − points	2-year total mortality ..... Cardiac syncope probability	2% score <3 21% score ≥3 ..... 2% score <3 13% score 3 33% score 4 77% score >4

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

[a]Nausea/vomiting

[b]Warm-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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Outcomes of Medical Emergencies on Commercial Airline Flights

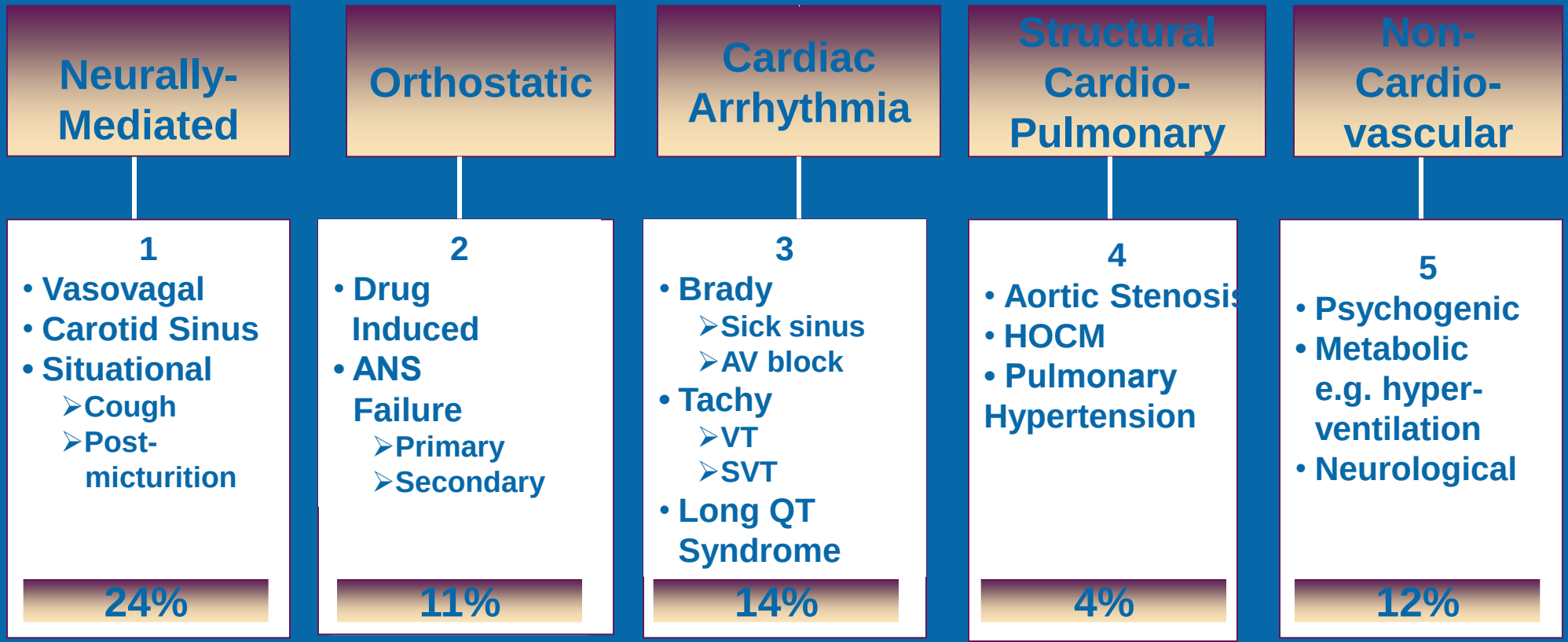
Drew C. Peterson, M.D., Christian Martin-Gill, M.D., M.P.H., Francis X. Guyette, M.D., M.P.H., Adam Z. Tobias, M.D., M.P.H., Catherine E. McCarthy, B.S., Scott T. Harrington, M.D., Theodore R. Delbridge, M.D., M.P.H., and Donald M. Yealy, M.D.

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).

N Engl J Med 2013;368:2075-83.

Syncope: Etiology



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

Younger Patient

- Vasovagal
- Situational
- Psychiatric
- Long QT*
- Brugada syndrome*
- WPW syndrome*
- RV dysplasia*
- Hypertrophic cardiomyopathy*
- Catecholaminergic VT
- Other genetic syndromes

Older Patient

- Cardiac**
  - Mechanical
  - Arrhythmic
- Orthostatic hypotension
- Drug-induced
- Neurally mediated
- Multifactorial

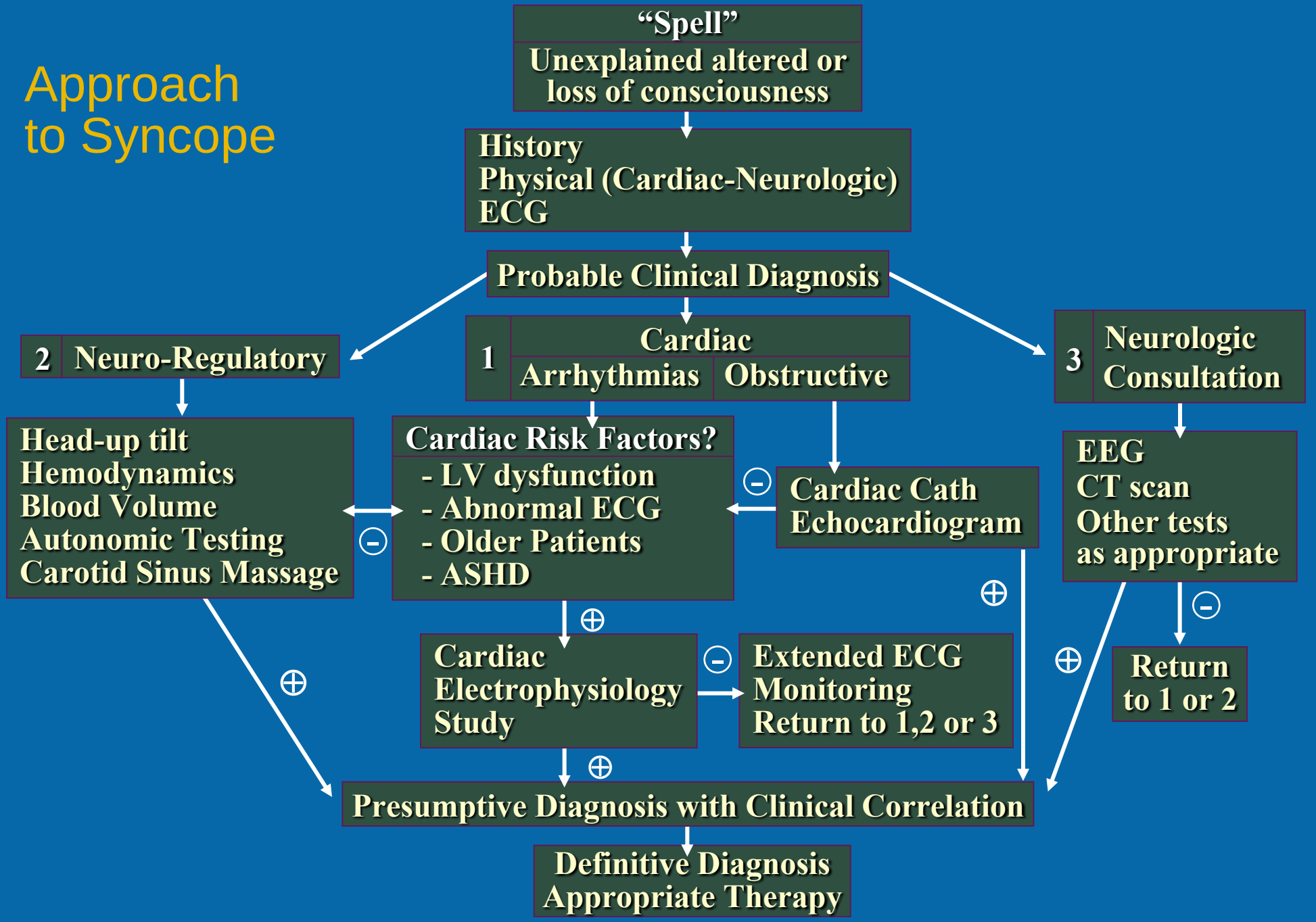
Underlined: benign
*Rare, not benign
**Not benign

Olshansky B. In: Grubb B and Olshansky B. eds. *Syncope: Mechanisms and Management*. Futura. 1998:15-71.

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



From: New Concepts in the Assessment of Syncope

J Am Coll Cardiol. 2012;59(18):1583-1591. doi:10.1016/j.jacc.2011.11.056

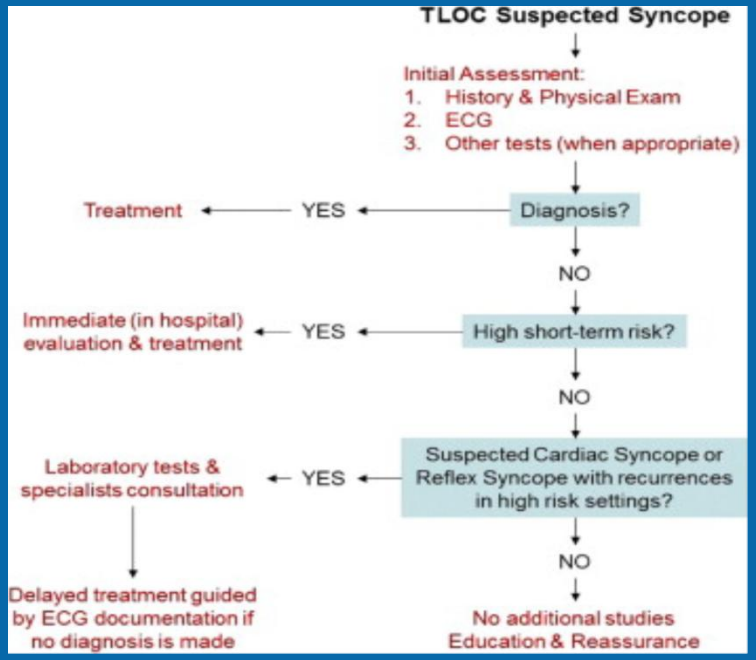


Figure Legend:

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

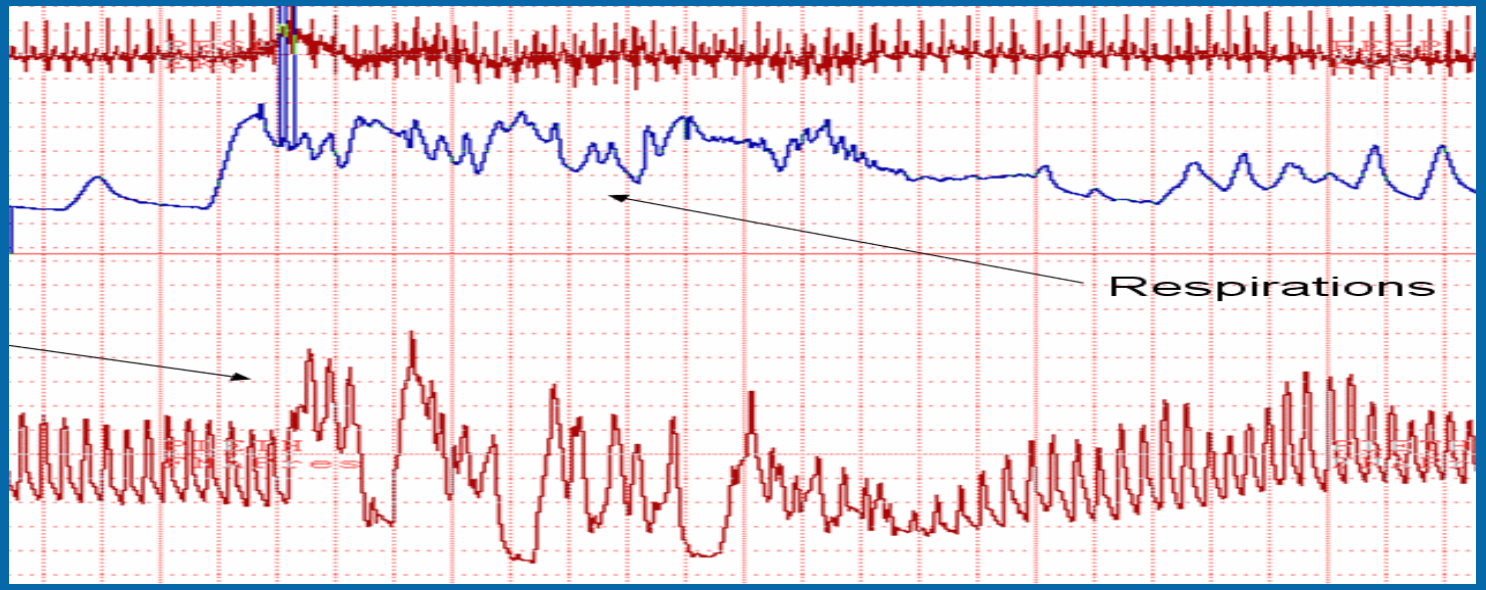
- Cardiology/EPS Referral – Cath, EP study, ILR

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, occassional 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

Calkins AJM 1995

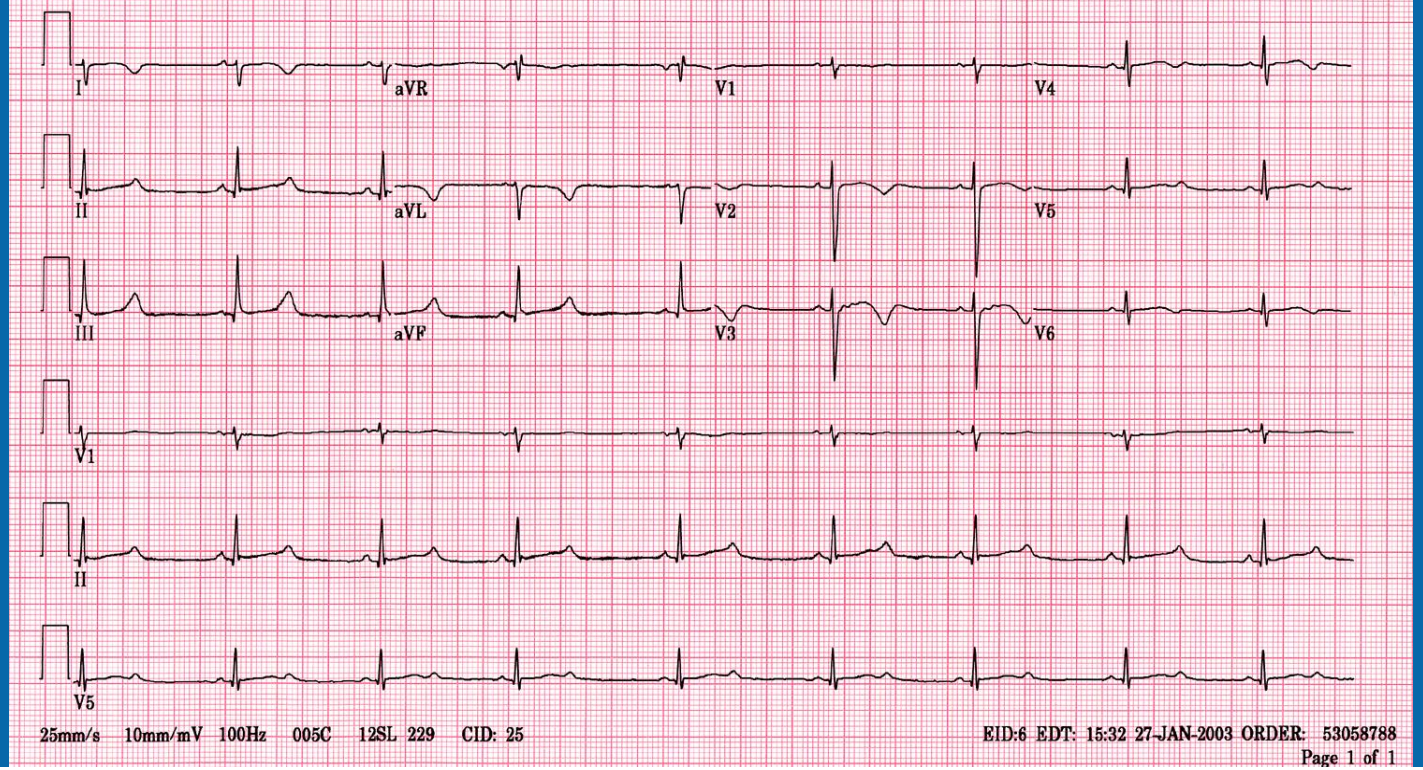
Syncope - Clues from the History

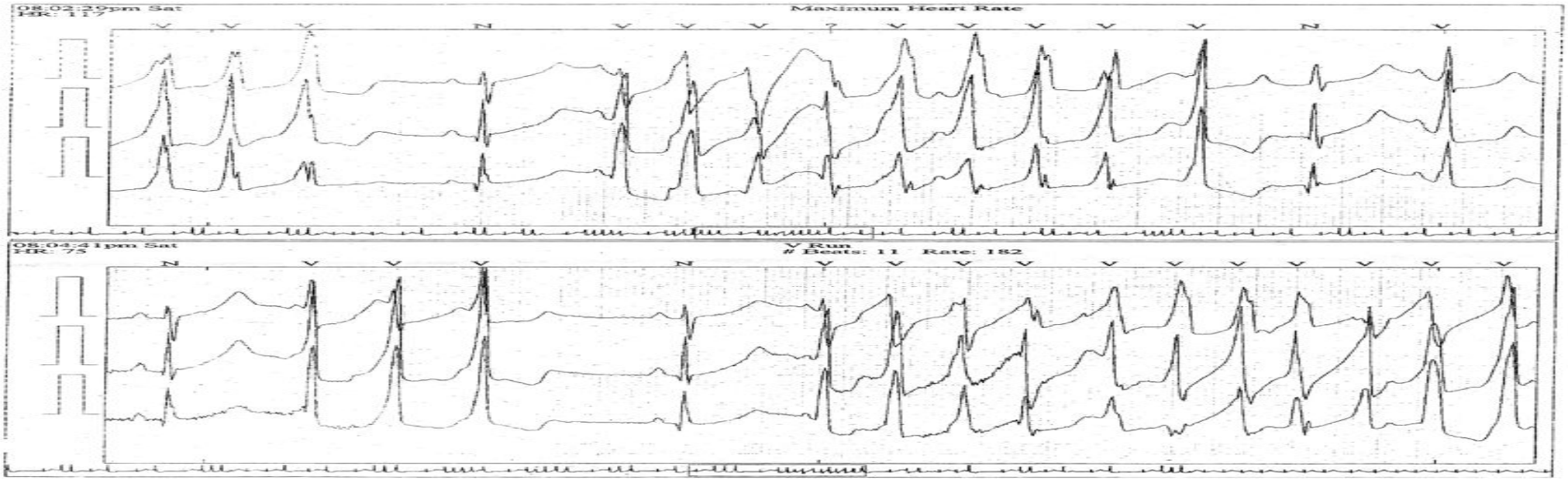
- Family History of SCD = LQTS, Brugadas, HCM, ARVD/C ? Drownings, ?MVAs
- Tongue biting, incontinence = Seizure
- Motion sickness, migraines, childhood fainting, athlete, hypervagotonia, early repolarization on EKG, Family Hx of fainting, phobic/pain fainting = Vasovagal
- Head turning = Carotid sinus 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

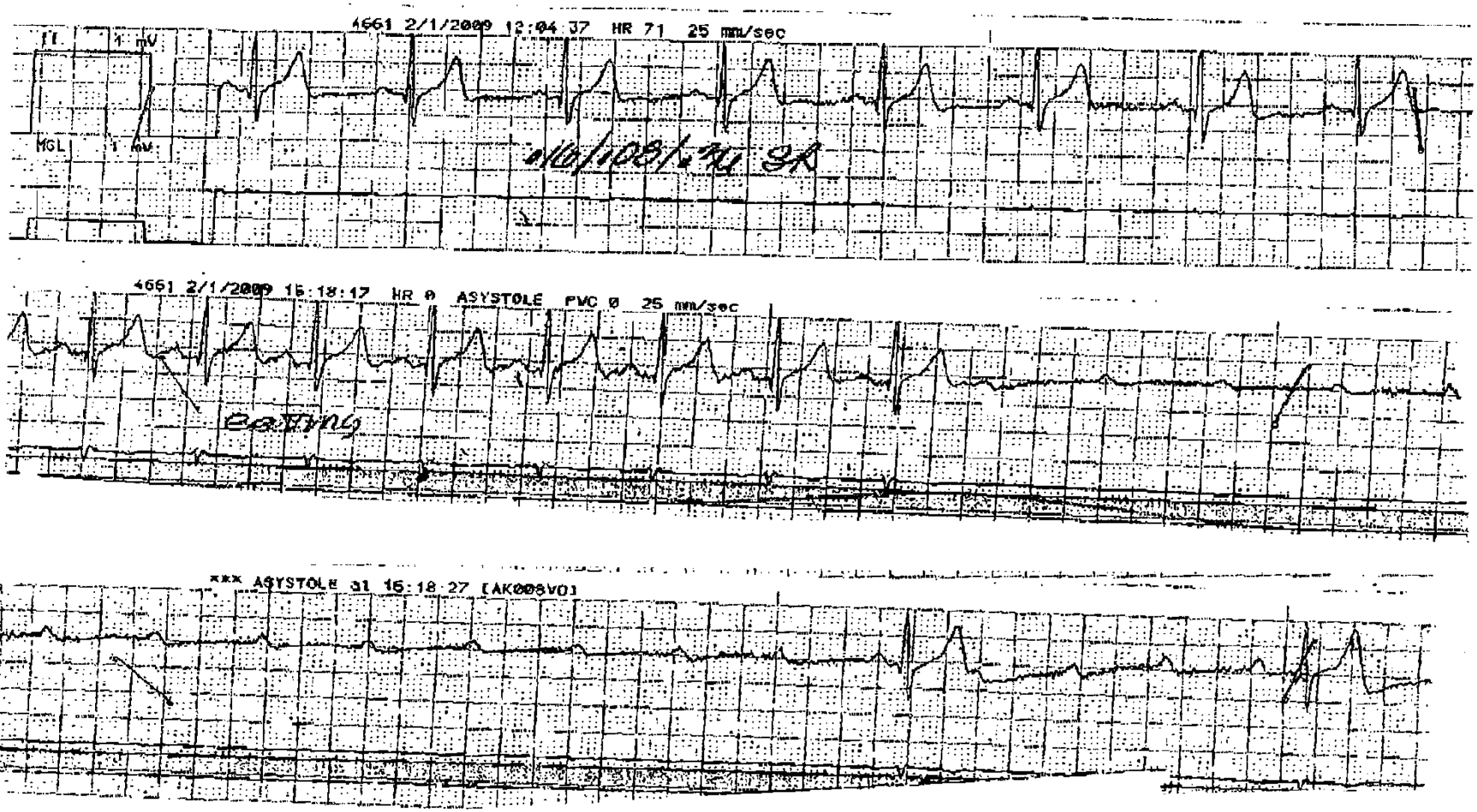
- Syncope in AM, with rapid standing, post prandial
- Systolic drop 20-30 mmHg , diastolic drop 10 mmHg or SBP< 90 although usually much more clinically
- Most common secondary causes – DM, Medications, Volume depletion
- Primary autonomic failure relatively rare and usually obvious - Parkinsons, cancer/paraneoplastic,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

LQTS

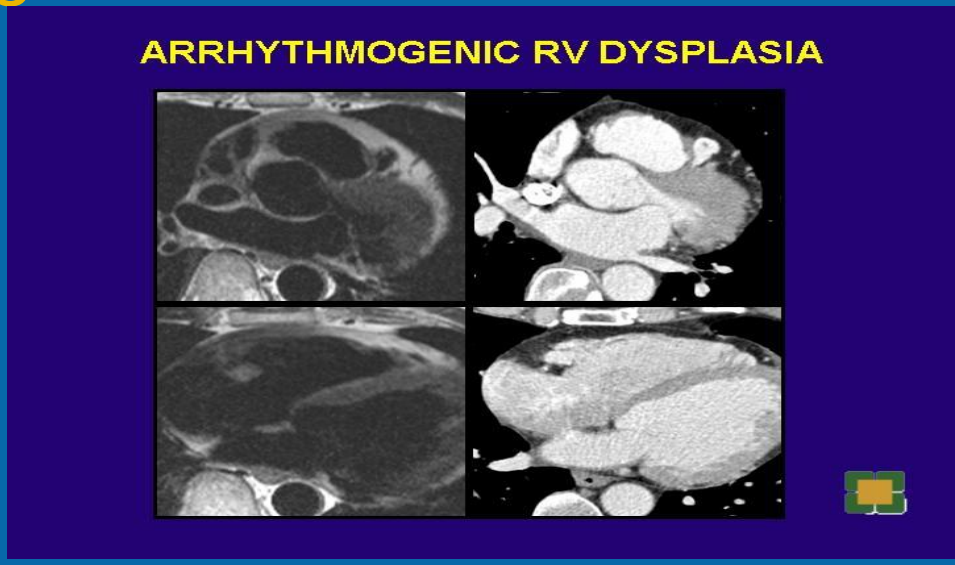

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5
25mm/s 10mm/mV 100Hz 005C 12SL 229 CID: 25
EID:6 EDT: 15:32 27-JAN-2003 ORDER: 53058788
Page 1 of 1


08:02:39pm Sat
HR: 117
Maximum Heart Rate
08:04:41pm Sat
HR: 75
V Run
Beats: 11 Rate: 182

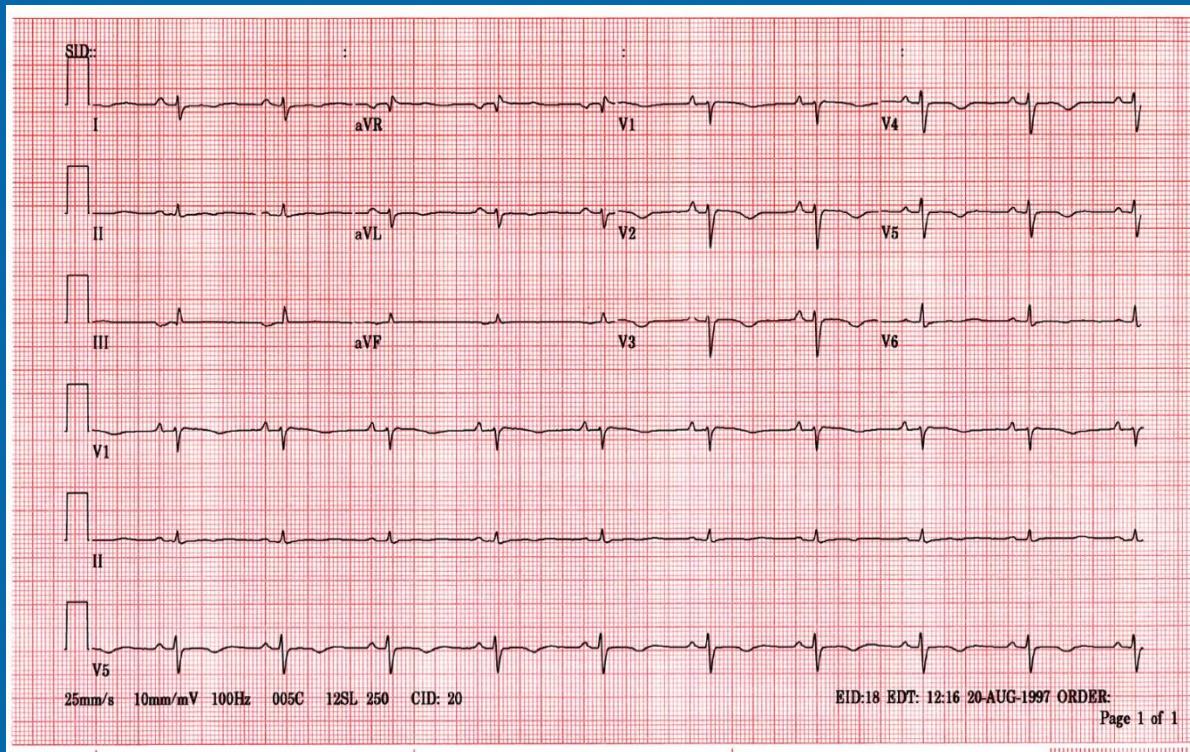
Deglutition/ Swallow Syncope



ARVD – Arrhythmogenic Right Ventricular Dysplasia

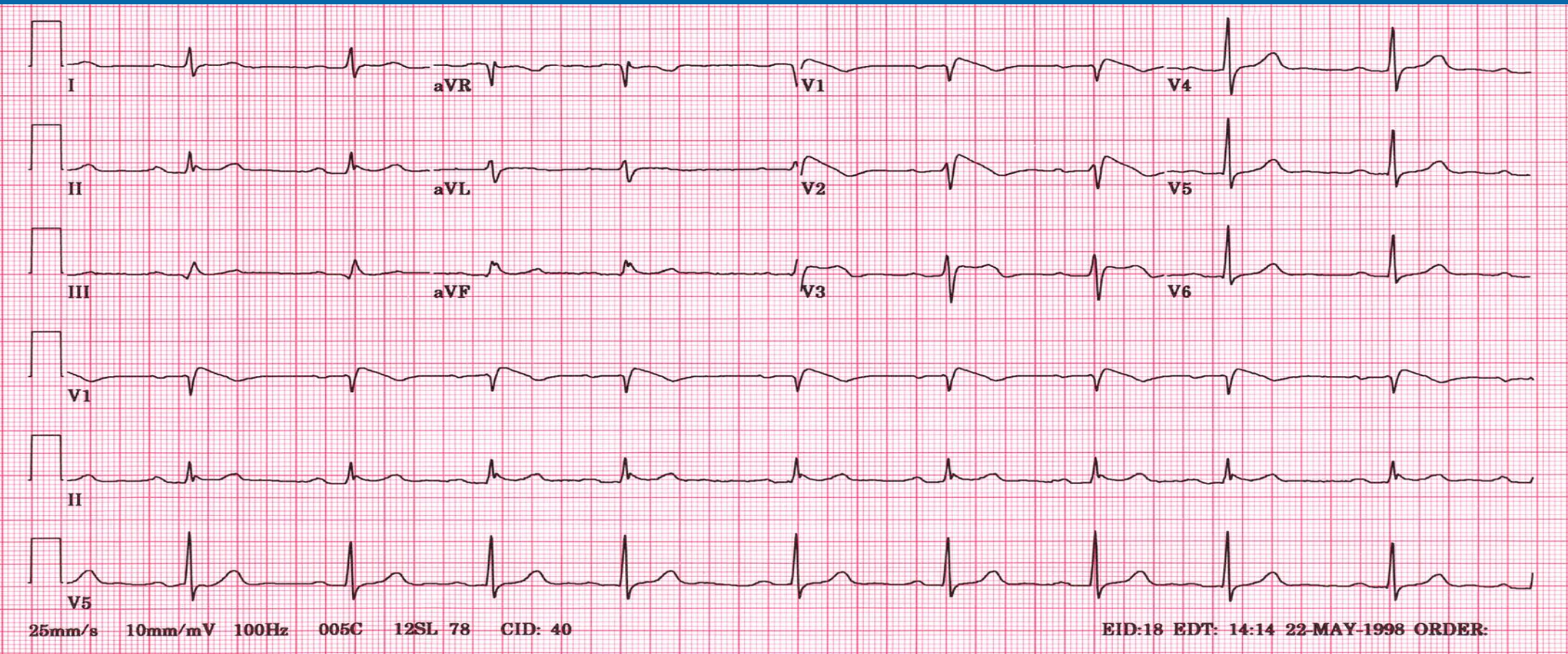


- RBBB/ epsilon waves, t - wave abnormality - “juvenile t wave pattern”
- Fatty - fibrous infiltration of right ventricle
- Characteristic findings of fatty infiltration on CT/MRI
- Syncope due to SMVT or PMVT
- Genetic testing
- ICD, AAD, RFA if syncope or SCD

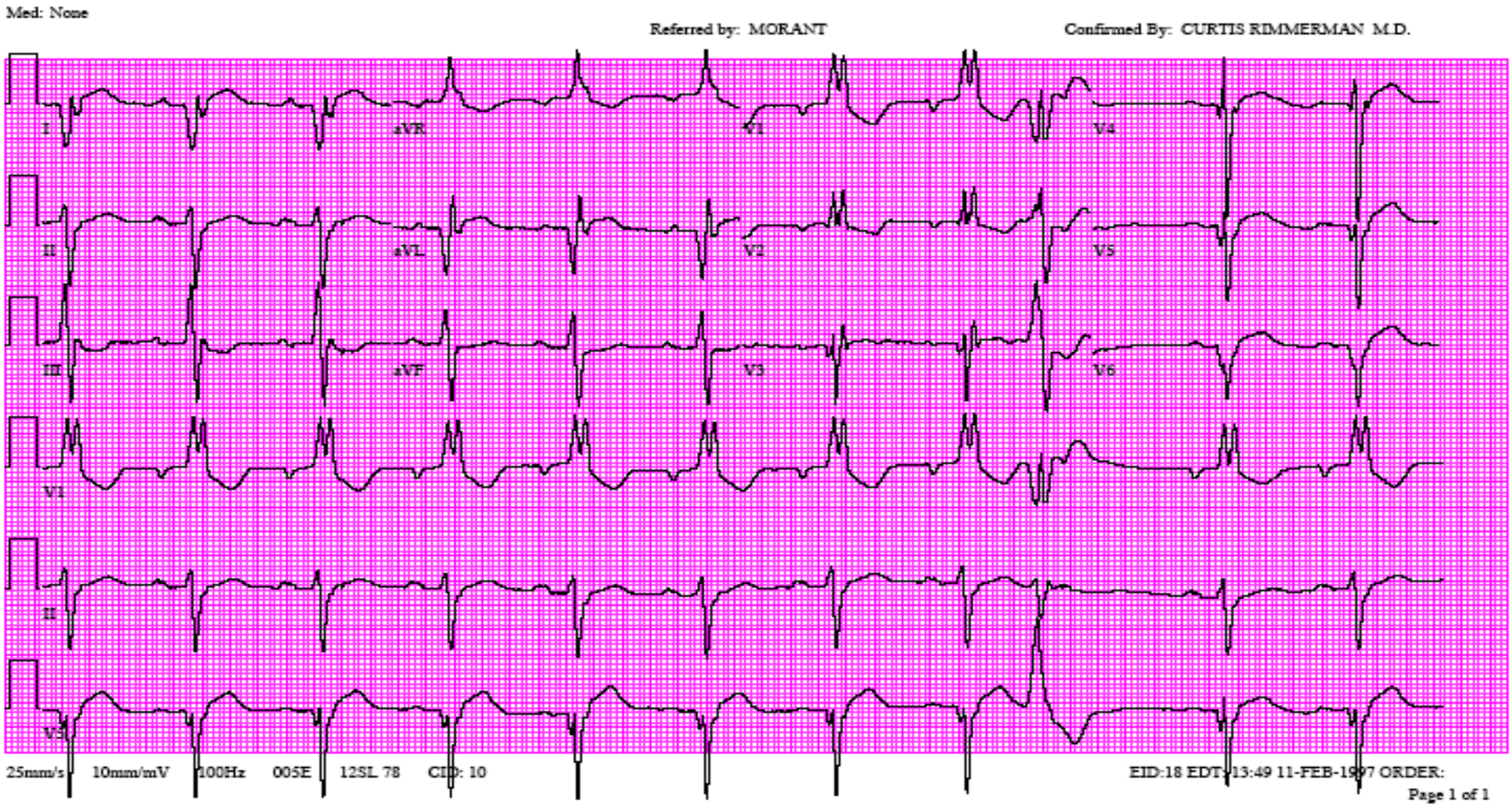


Brugada's Syndrome

- Channelopathy with VT/VF
- RBBB and ST segment elevation in anterior precordial leads
- Genetic testing – Familion
- Flecainide or Procainamide challenge



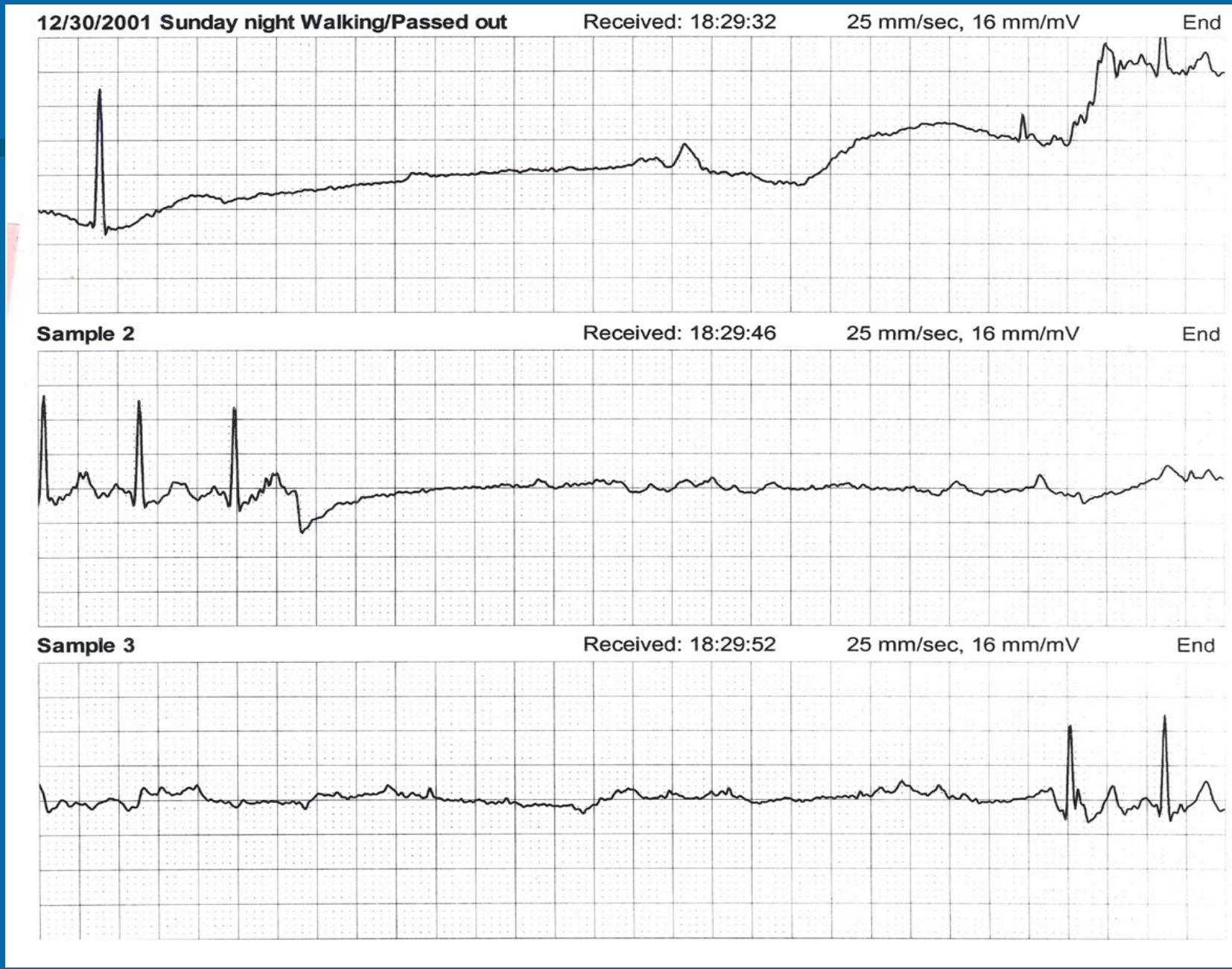
Trifasicular Block – RBBB,First degree AV block,LAHB



Syncope – EKG monitoring

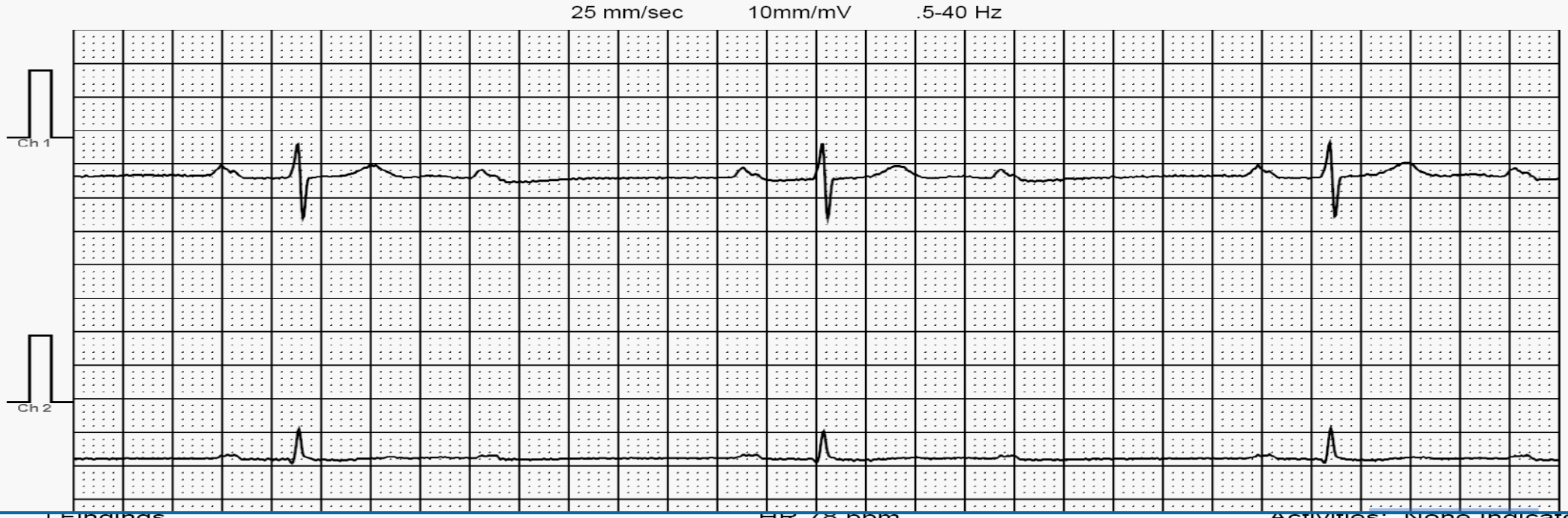
- **Holters – useless unless something happens**
- **Event recorders - continuous loop recorder**
- **Implantable**
  - **Reveal and Confirm - inplantableloop recorder**
  - **Pacemakers/ ICDs with wireless transmission**
- **Ambulatory Wireless long term monitoring for diagnosis/prevention – MCOT (Mobile Cardiac Outpt Telemetry) continuous loop recorder using cellular networks, bluetooth e.g. Cardionet, Lifewatch**
- **Future devices will incorporate BP,O2 etc**

Fig. 2. The original Holter biotelemetry apparatus in 1947 weighing 85 lb (38 kg) (from ref. [2]).


12/30/2001 Sunday night Walking/Passed out
Received: 18:29:32
25 mm/sec, 16 mm/mV
End
Sample 2
Received: 18:29:46
25 mm/sec, 16 mm/mV
End
Sample 3
Received: 18:29:52
25 mm/sec, 16 mm/mV
End

Urgent - 2nd Degree AVB,Type 2, Dr. Moualla notified

Symptoms: None Indicated



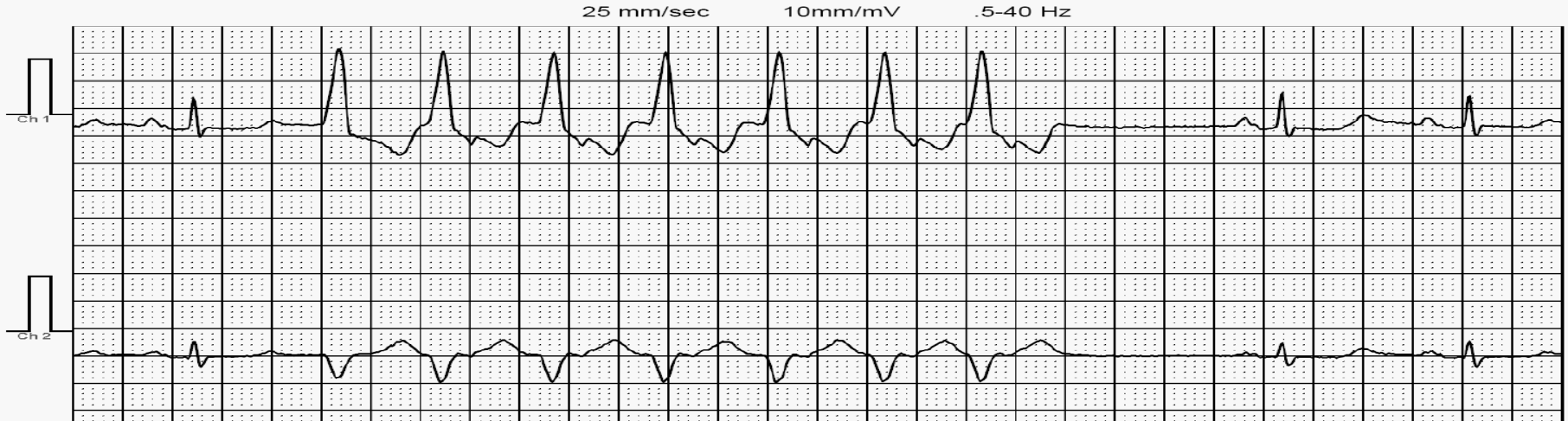
Findings

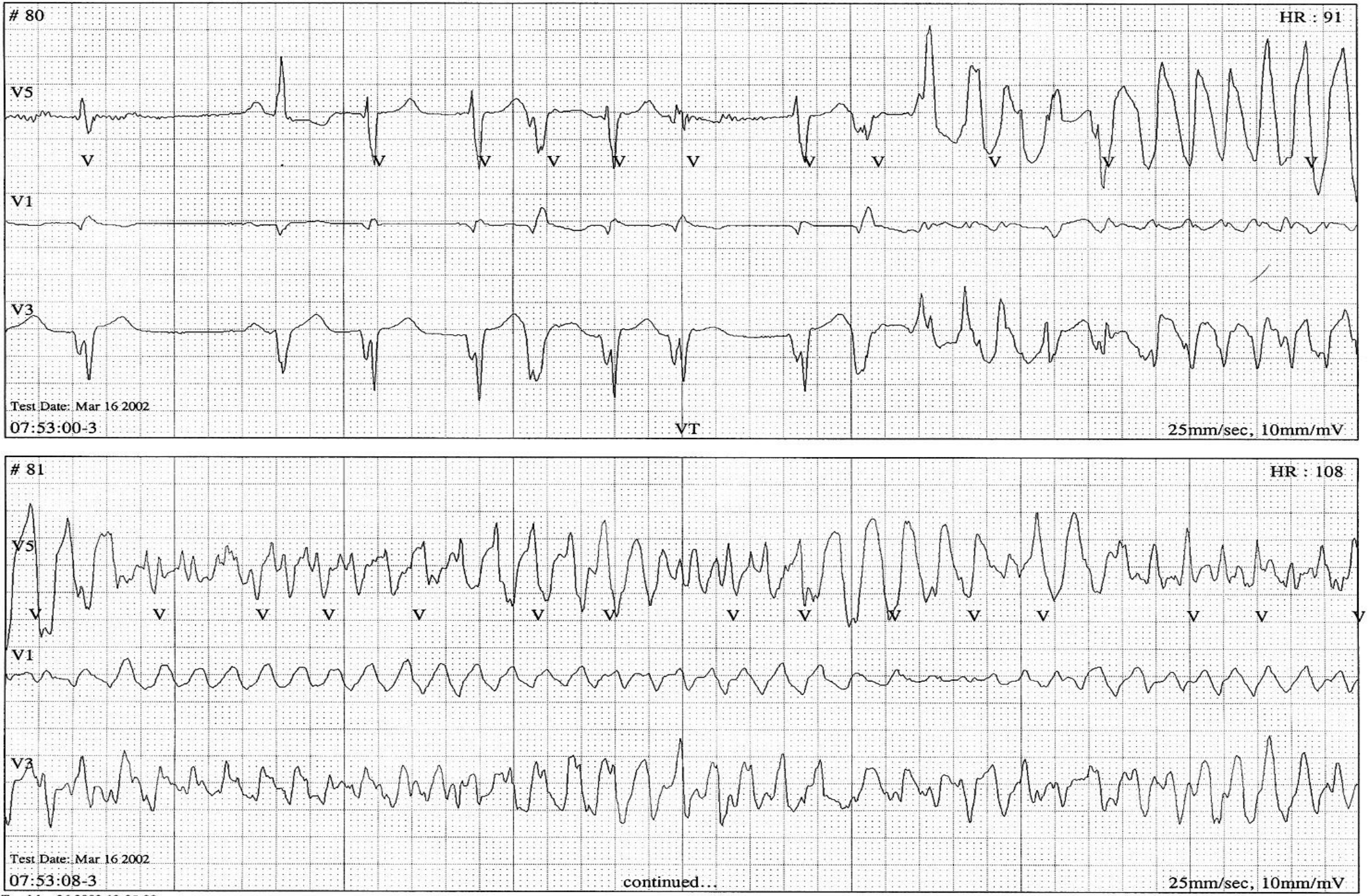
HR 78 bpm

Activities: None Indicated

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

Symptoms: None Indicated




80
HR : 91
V5
V1
V3
Test Date: Mar 16 2002
07:53:00-3
VT
25mm/sec, 10mm/mV
81
HR : 108
V5
V1
V3
Test Date: Mar 16 2002
07:53:08-3
continued...
25mm/sec, 10mm/mV

Wireless Ambulatory ECG Monitors

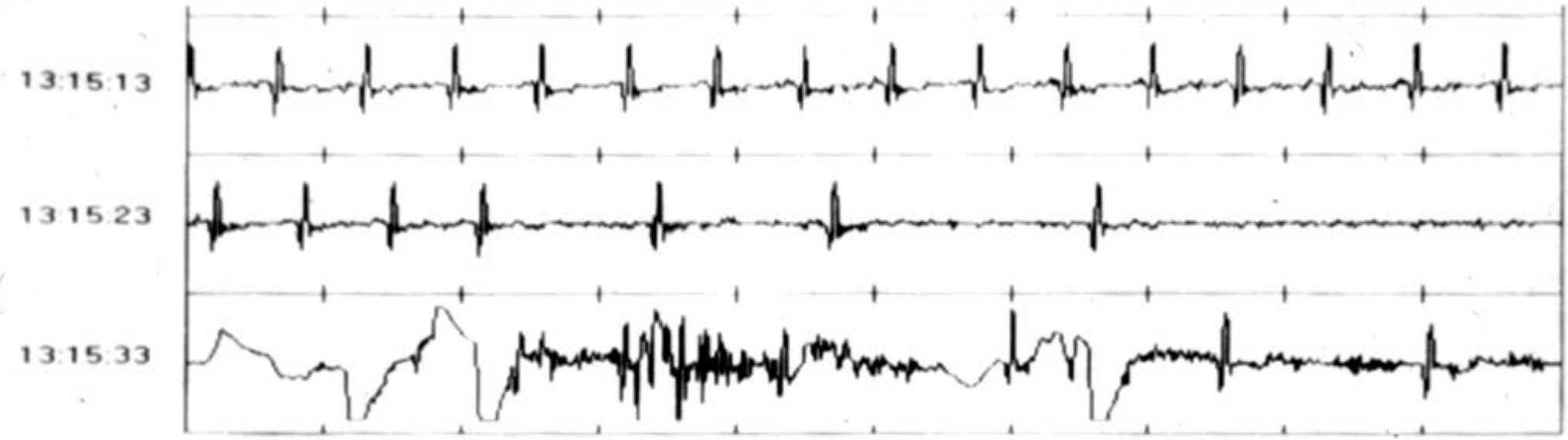
- CardioNet , Lifewatch, others
- Automatic/ Patient activated
- External 3 Lead/Portable Monitor Wireless Connection to Service
- GPS Capable, Altimeter
- Aimed at Low Risk Patient - Not in 911 business
  - Atrial fibrillation
  - SVT
  - SSS
  - Syncope of Undetermined Origin
  - Cryptogenic Stroke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

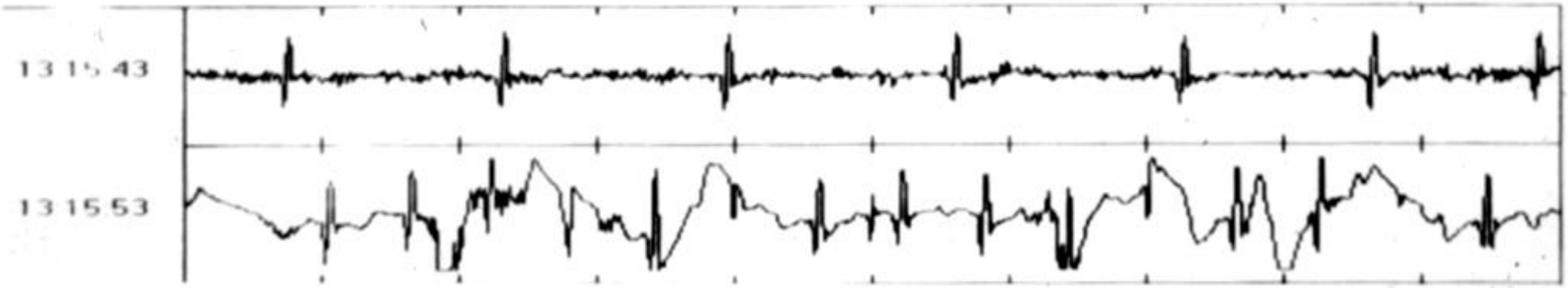
Reveal/Reveal Plus/ DX /XT - Medtronic Insertable Loop Recorder -ILR

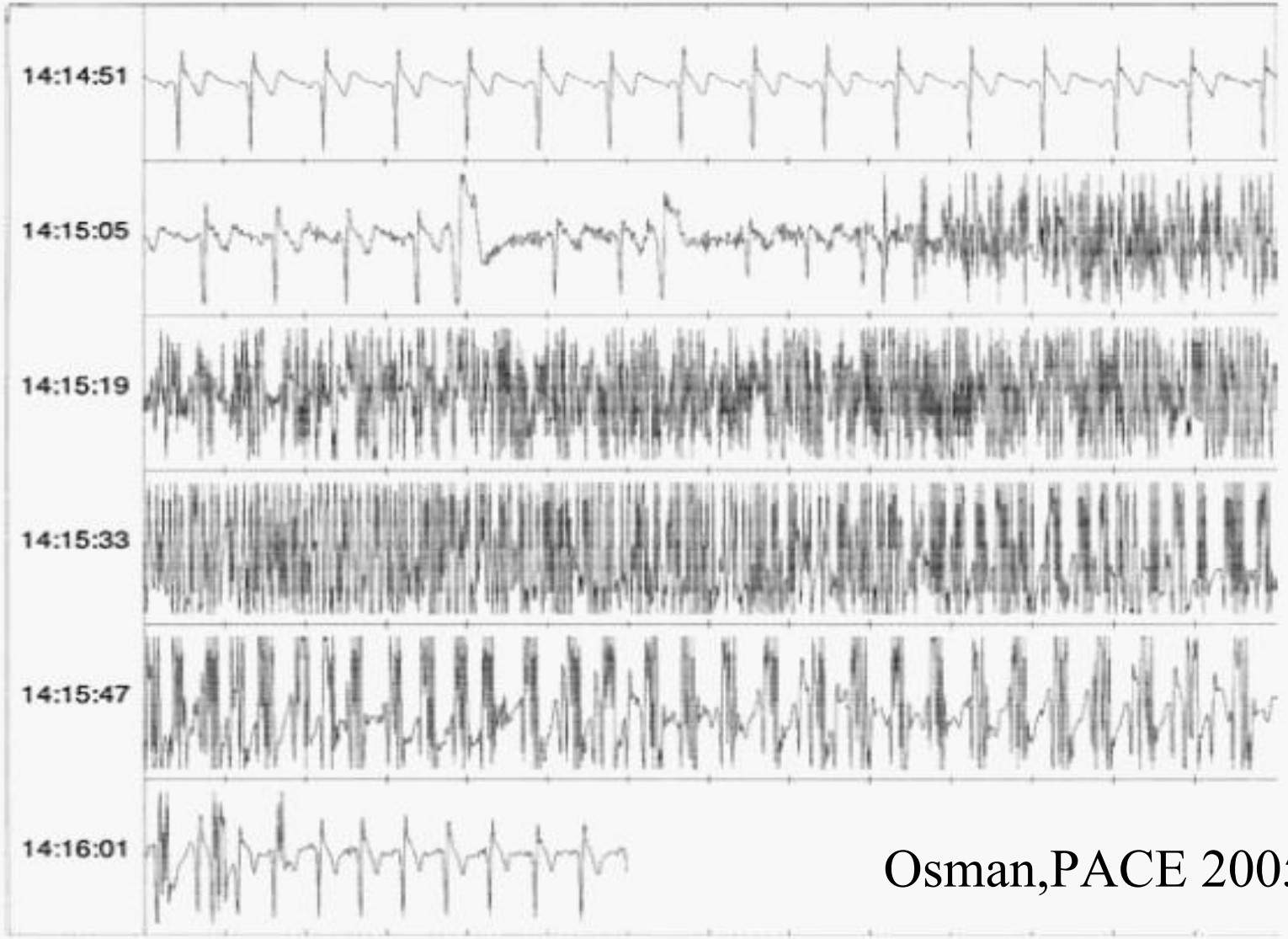
- Records EKG – not electrogram
- Minimal Incision – Low Risk
- Appropriate Patient Selection –early utilization
  - Syncope in Normal Hearts
  - Fleeting Suspected SVT's
  - Drug Refractory Seizures
  - Cryptogenic CVAs
- Inappropriate for High Risk Patients
  - Severe LV/Post MI
  - VT Suspected
  - Structural Heart Disease



Reveal(tm) Model 9525 12 47 02/23/1999
Gain x8 (+/- 0.2 mV) Programmer 9790 9802E01
Storage Mode: C - 3 events (6 min pre / 1 min post) (c) Medtronic Inc 199
Event 1 of 2 recorded 02/01/1999 Page 4 of 6

12.5 mm/sec, 25.0 mm/mV





Osman,PACE 2005

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

Syncope Strategies – Cost Comparisons

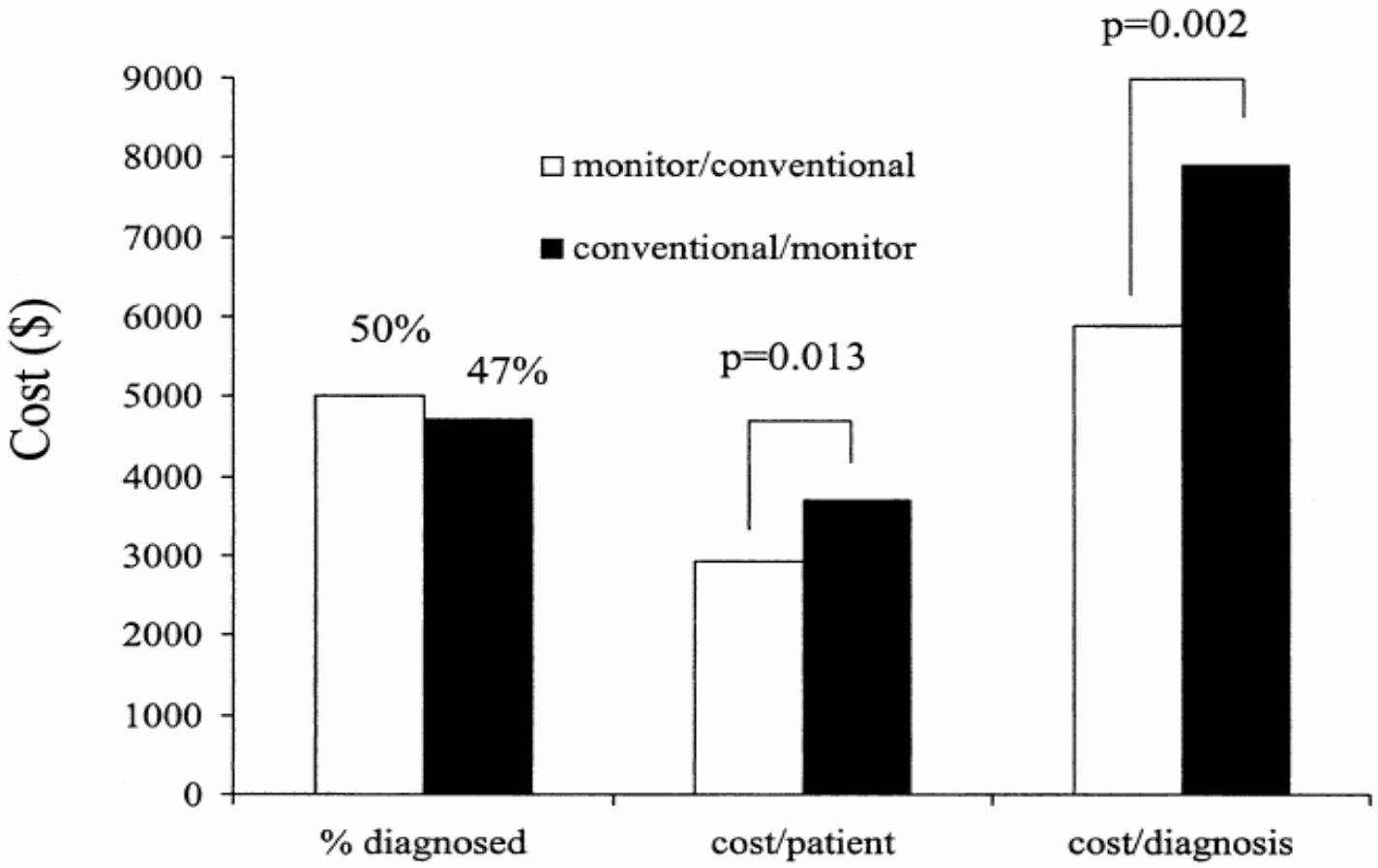


Figure 2. Cost and diagnostic yield of the two treatment strategies. The results of the testing strategy are shown for all patients in the trial, including those who crossed over. The overall diagnostic yield of the two strategies was comparable, but the cost per diagnosis of the strategy of primary monitoring was significantly reduced by $2,016 ($p = 0.002$).

Krahn JACC 2003

Medtronic Reveal LINQ

ISSUE 3 – ILR Guided Pacemaker Implantation

Arrhythmia/Electrophysiology

Pacemaker Therapy in Patients With Neurally 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. Krahn, 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

Brignole Circulation 2012

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 symtpoms
- Pacemaker programed on or off
- 57% recurrence with PPM off
- 25% recurrence with PPM on

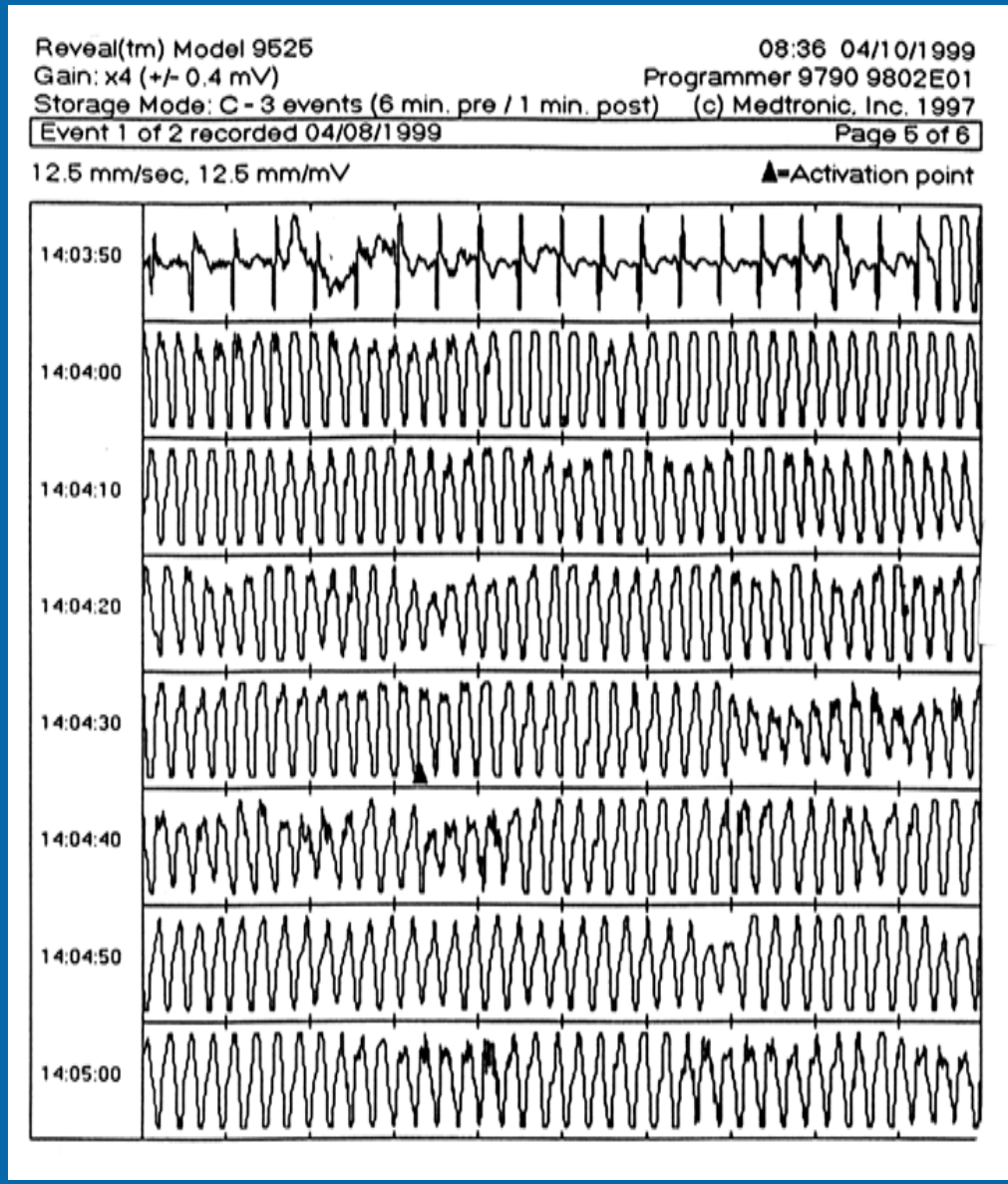
Brignole Circulation 2012

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



Syncope

- 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 t least one episode**
- **ANS pertubations - 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

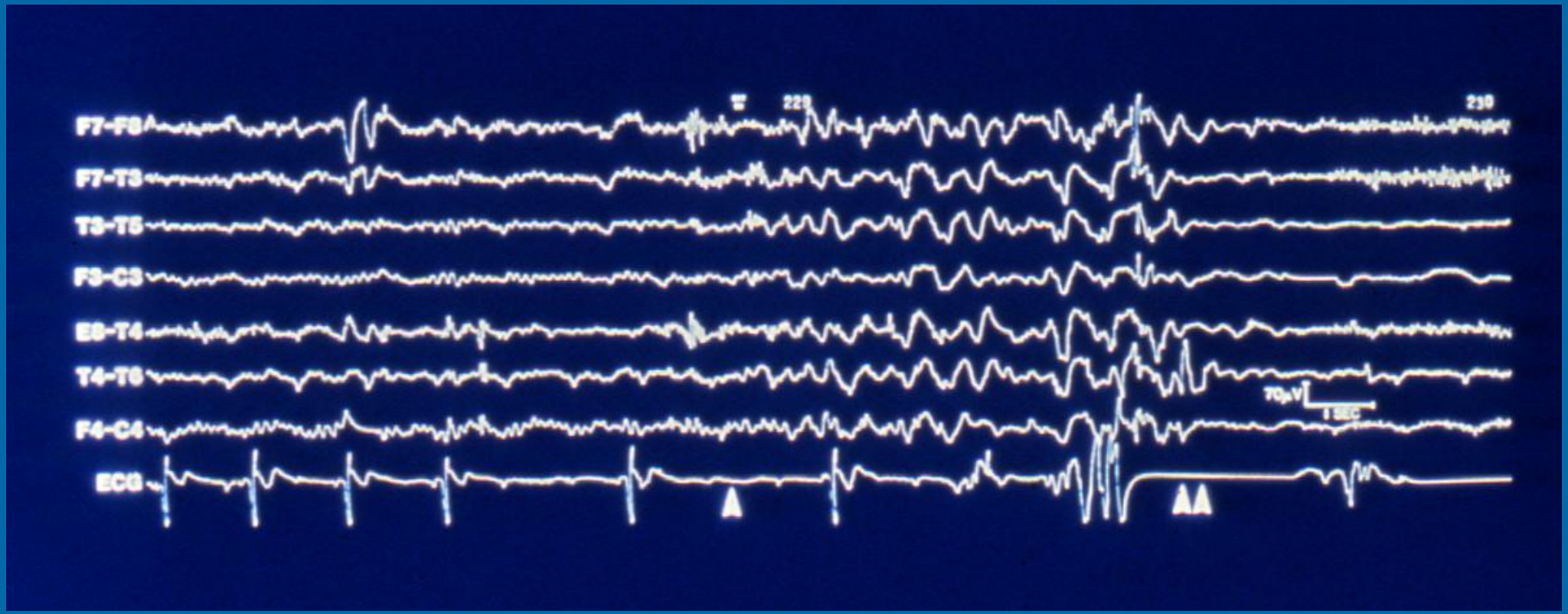
Genetic Basis for Vasovagal Syncope

- 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

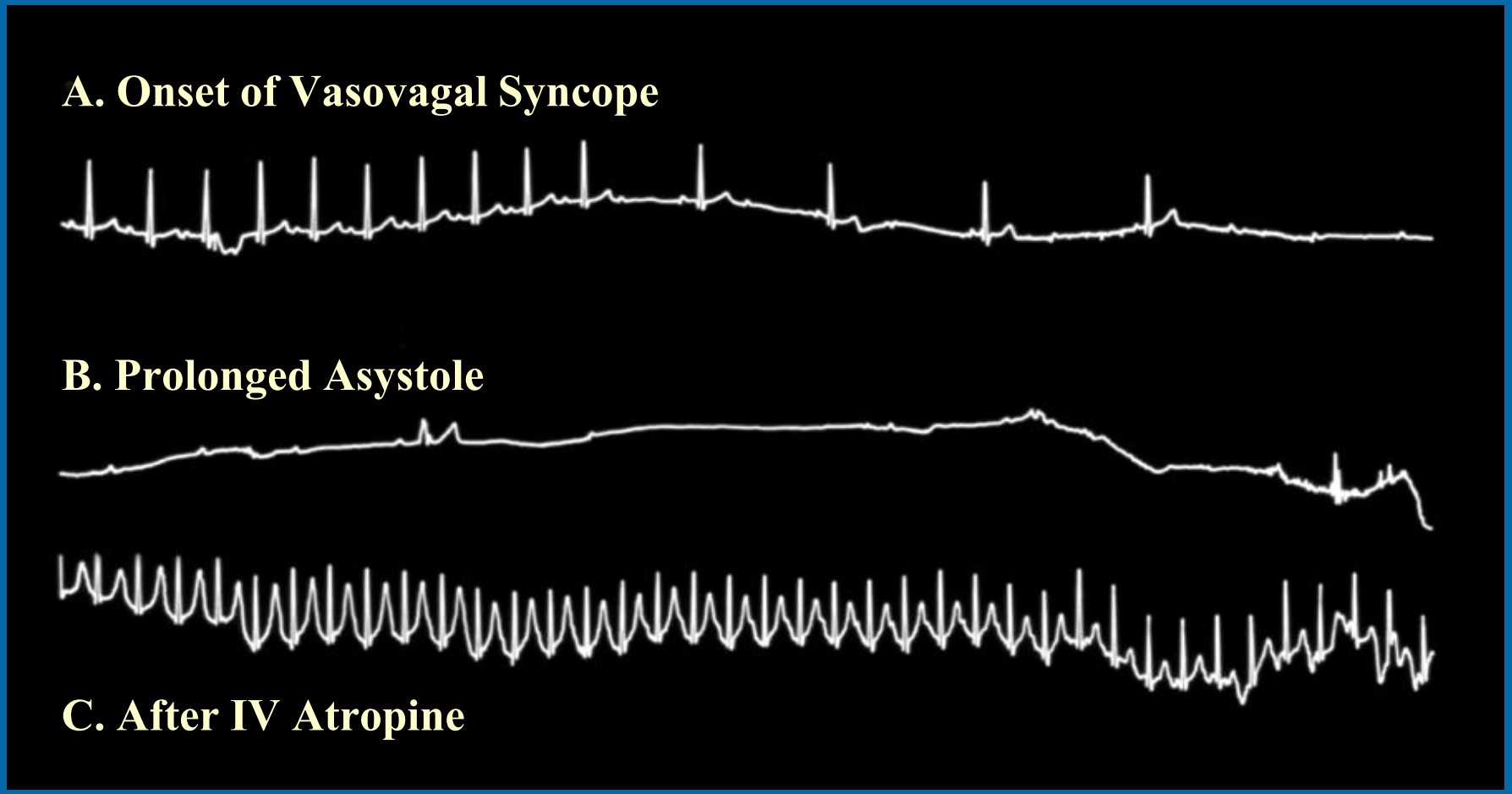
Tilt Table Test

- 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



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

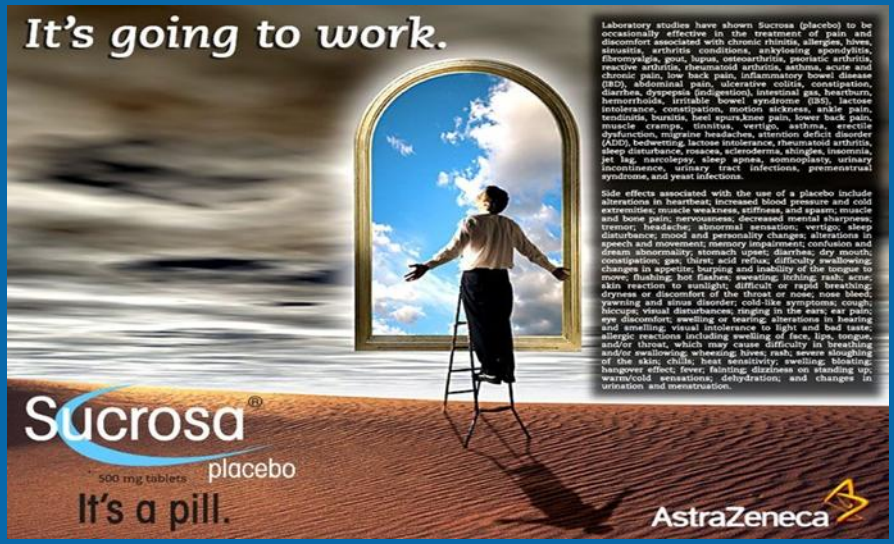
- Reassurance / Recognition / Avoidance
- Increase salt/ electrolyte fluids - 5-7 grams per day / florinef
- Physical Countermeasure Maneuvers (PCM) Supine position, Leg Crossing, Muscle tensing Circ 2002 Coughing
- Jobst / physical therapy / Avoid deconditioning
- Serial tilt testing not predictive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

Figure 1. Leg crossing and muscle tensing during tilt-table testing. The maneuver consists of crossing the legs in standing position with tensing of leg, abdominal, and buttock muscles. The legs are thus firmly squeezed together (person is a stand-in).

Recommendations: treatment of reflex syncope

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

[a]Class of recommendation.
[b]Level of evidence.
CSS = carotid sinus syndrome; PCM = physical isometric counterpressure manouuvre; 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/Maneuvers(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.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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 Klingenheben, Andrew Krahn, Carlos Morillo, Mario Talajic, Teresa Ku, Fetnat 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

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
- Metoporolol 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

Raj Prog CV Dis 2013

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 DecadesFirst and Only FDA Approved Therapy to Demonstrate Symptomatic Benefit in Patients with NOH

BusinessWire
A Berkshire Hathaway Company

CHELSEA THERAPEUTICS

CHARLOTTE, N.C., Feb 18, 2014 (BUSINESS WIRE) -- Chelsea Therapeutics International , Ltd. CHTP -0.88% today announced that the U.S. Food and Drug Administration (FDA) granted accelerated approval of NORTHERATM (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

BETHESDA, 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 nondiabetic 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
- Significant Risk of Severe Nocturnal HTN and Stroke/MI/Renal failure. Monitor closely.
- 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

Brignole JACC 2011

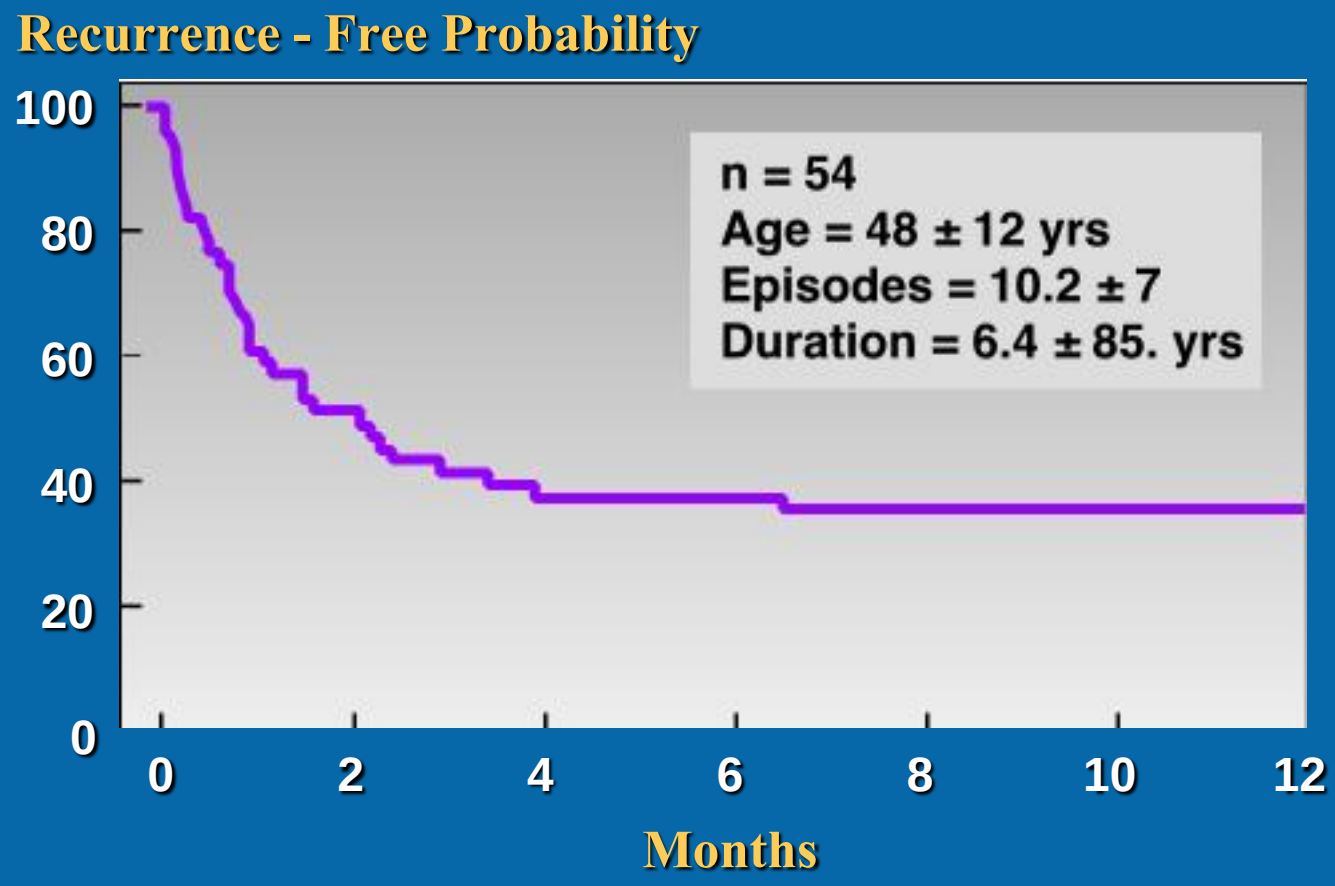
Syncope without Prodrome in Normal Heart and Normal EKG

- 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

Brignole JACC 2013

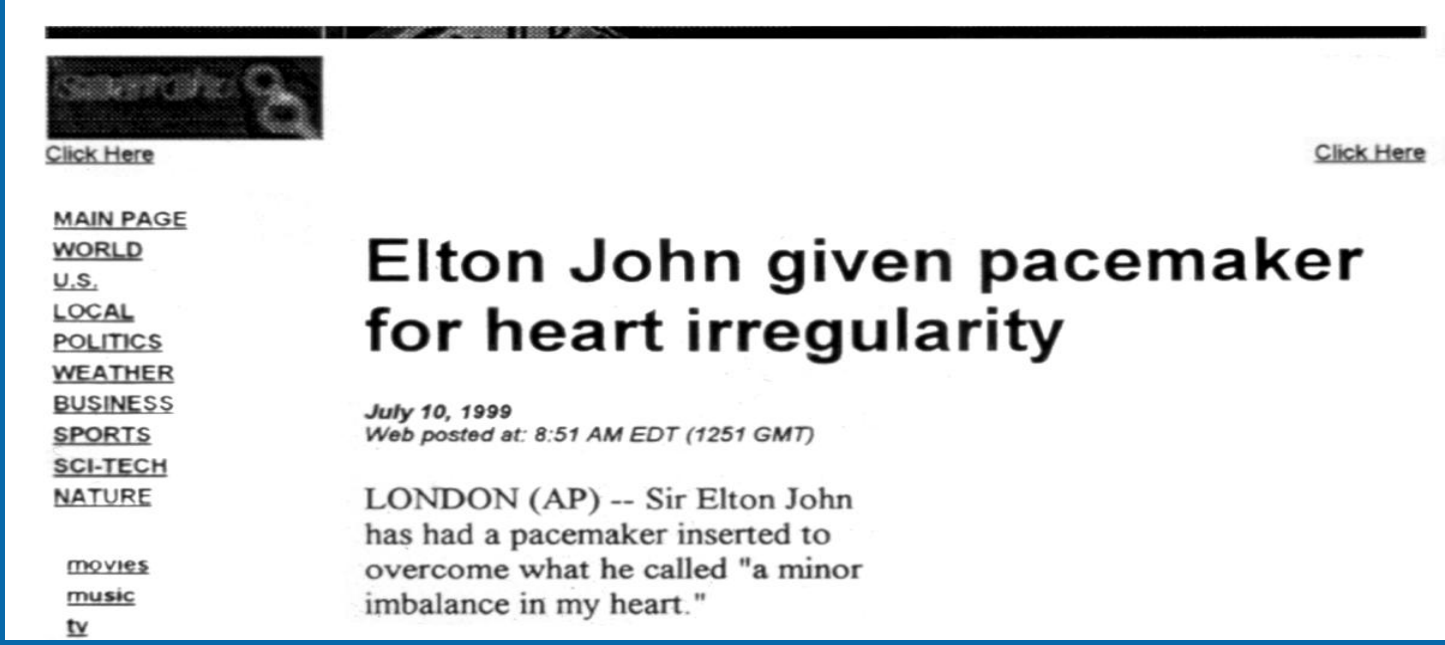
Natural History of Neurocardiogenic Syncope

Spontaneous Resolution in Untreated Patients



Natale, AJC 1995

Pacemakers for Vasovagal Syncope



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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."

- 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

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"**
- **EGSYS, 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 - Trifasicular 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 Cardioloy Clinic 2013