Beyond Hypertensive and Arteriosclerotic Cardiovascular Disease

ALTERNATIVE CAUSES OF SUDDEN CARDIAC DEATH
Introduction

Doolan, et al., 2004

Nine year review of SCD in those over 35

- 24% ASCVD
- 15% HCM/Idiopathic LVH
- 12% Myocarditis
- 7% Complications of congenital heart disease
- 3% ARVD
- 31% “Primary arrhythmogenic disorders” NOS
The autopsy begins at the scene . . .

- Thorough scene investigation
- Obtain relevant medical records
- These cases may warrant a discussion with the PCP
Systematic Examination of the Heart

Weight
- Correlated with body weight (0.05% TBW in kg)
- Correlated with height (after Zeek)
  - Male: height (cm) x 1.9 - 2.1 (+/- 40 gm)
  - Female: height (cm) x 1.78 - 21.58 (+/- 30 gm)

Cardiac chambers
- Hypertrophy
- Scarring and/or recent infarction
- Thinning
- Fatty replacement
- Pericardial/endocardial thickening
- Dilation
- Intramyocardial lesions
- Alternative longitudinal (4-chamber) approach
Systematic Examination of the Heart
Systematic Examination of the Heart

- Valves
  - Base along path of blood flow or parallel cut above the valve in question
  - Stenosis
  - Redundancy
  - In asymmetrical septal hypertrophy seek sub-aortic mitral impact lesion

- Epicardial coronary arteries
  - Origin/ostia
  - Course
  - Caliber
Systematic Examination of the Heart

- Conduction system
  - SA node
    - Anterolateral junction of SVC/RA surrounding small atrial artery
  - AV node
    - Right side of interatrial septum, anterior to coronary sinus and posterior to the membranous IV septum
  - His bundle
    - Penetrates central fibrous body to upper margin of muscular IV septum
Conduction System of the Heart
Coronary Artery Anomalies

- Illustrative cases
- Incidence
- Classification
Case 1

- 42+ week pregnancy, G₂P₁
- Unremarkable prenatal course
- Delivery by repeat C/S, Apgars 8/9
- Observed by nurse at 48 hours of age pale and apneic - never cyanotic
- “Flat-line” throughout 20-minute resuscitation attempt
Autopsy

- “Post-dates” appearance, no dysmorphic features
- Liver edge palpable 3 cm below right costal arch
- Wt. 2,850 gm (10%ile); L 51 cm (50%ile); OFC 34 cm (25%ile)
- Normal left ventricle, no ductal dependent structural anomaly, however . . .
Case 1

- Levocardia with normal atrioventricular and ventriculoarterial alignments
- Obliquely probe patent foramen ovale via the right atrium
- Unremarkable tricuspid valve, right ventricle and pulmonary valve
- Normal bifurcation of main pulmonary artery trunk
Case 1

- “Tight” ductus opened longitudinally revealing prominent intimal pads
- Normal venous return
- Unremarkable left atrium, mitral valve, left ventricle and aortic valve
- Normal distribution of epicardial coronary arteries
- Stenotic, slit-like left coronary ostia
Case 2

- 8-year-old boy playing basketball
- Complained of feeling tired, sat at base of basketball hoop.
- Slumped over, CPR initiated by bystanders
- PMHx: two seizures as a toddler, on carbamazepine until seizure-free for one year, off meds for $2\frac{1}{2}$ years.
Case 2

Focal endocardial thickening, LVOT
Case 3

- 57-year-old male returned home from 20 mile tandem bicycle ride with wife
- Mentioned “feeling bloated” during the ride
- Wife went upstairs for ~8 minutes and returned to kitchen to find he had vomited and was unresponsive on the floor
- Previously healthy, annual physicals
Case 3 - Autopsy

- 71 inches, 194 pounds
- Heart 520 gm, LVH
- Left dominant coronary arteries
  - 40% stenosis, mid-LAD
  - Small caliber circumflex
  - Markedly small caliber RCA with short course and marked ostial stenosis
Case 3
Case 4

- 13-year-old female on school snow-shoe outing, clear day temperatures in the 20’s
- “Easy” hike with “lots of stops”
- 2/3 into hike c/o posterior neck pain and shortness of breath
- Completed hike after a rest, but was crying on reaching the lodge with neck pain and SOB
- Witnessed arrest with CPR started immediately
Case 4

- Asystolic throughout prolonged resuscitation effort.
- Similar episode of posterior neck pain and SOB during soccer practice previous fall
- Has healthy 14-year-old female sibling
Case 4 - Autopsy

- 66 inches, 145 pounds, Tanner III-IV female
- Sparse petechiae over eyelids
- CNS, liver, GI, GU and endocrine systems unremarkable
- Right and left lungs 760 and 680 gm, diffuse hemorrhagic edema
- Odd appearance of left ventricular outflow tract
Case 4

- **Histology**
  - Marked myocyte nuclear enlargement
  - Hypereosinophilia, smudged cross-striations, wavy fibers,
  - Focal contraction band necrosis
  - Scout sections of nodal regions unremarkable
Coronary Artery Anomalies

- Variations in coronary anatomy are common
- “Atypical,” “abnormal,” “aberrant,” “anomalous,” “accessory,” “ectopic,” “incidental,” “variant” often unclear
- “Anomalous” or “abnormal” are used to define any variant observed in less than 1% of the general population
Frequency of Anomalies

- Higher incidence in young victims of sudden death than adults (4-15% vs 1%)

- Most common variants:
  - Split RCA (1.23%)
  - Ectopic origin of RCA near right aortic sinus (1.13%).

- Many variations, e.g. intramural extension or myocardial bridging of LAD, (5-25%), are so common they are not considered anomalous.
Literature on Anomalous Coronary Arteries

- Incidence 0.2% - 1.55% depending on case definition and study type.
- Literature dominated by individual case reports.
- Associated with cardiac/non-cardiac anomalies in > 50%.
- Risk of sudden death statistically declines beyond age 30.
Coronary Artery Anomalies

- Variability in coronary circulation
- Number and size of coronary ostia
- Positioning within sinuses
- Course of coronary arteries
Classification of Anomalous Coronary Arteries*

- Ectopic coronary origin
  - Pulmonary trunk
  - Aorta
  - Opposite coronary artery
  - Extracardiac vessel
  - Ventricular cavity
  - Other, e.g. truncus arteriosus

* From Lipsett, Cohle, Berry & Byard, Ped Path, 14:287-300, 1994
Embryonic Development of the Coronary Arteries

*Radial*, transmural “burrowing” of coronary angioblasts
Embryonic Development of the Coronary Arteries

*Oblique*, transmural “burrowing” of coronary angioblasts
Pulmonary origin 40%

Left coronary from pulmonary trunk
Hypoplasia 11%

Hypoplastic right coronary
Aortic origin 43%

- Left coronary from right sinus
- Right coronary from left sinus
- RCA arising from left sinus (probe)
Classification of Anomalous Coronary Arteries*

- Abnormal coronary artery size (atresia, hypoplasia)
- *Intrinsic coronary artery anomalies*
- Abnormal intramural course
- Abnormal distal connections or terminations

* From Lipsett, Cohle, Berry & Byard, Ped Path, 14:287-300, 1994
Hypoplastic Coronary Arteries

- Small luminal diameter (usually <1 mm) and reduced length.
- Often associated with the absence of the posterior descending coronary artery.
Intrinsic Coronary Artery Anomalies

Normal angle on left. Acute, vertical angulation on right. Note inferior ridge that may occlude ostium in diastole.

Superiorly displaced ostium with acute, vertical angulation of CA and incorporation of artery into aortic wall.
Coronary Artery Anomalies

- Mean age at death 2.2 years (4 hr–14 yr)
  - ACA from pulmonary trunk (75% dead before 12 months)
- Growth retardation in 50%
- 1:1.2 male:female ratio
- Cardiomegaly in 92% (>95%ile in 63%)
  - 100% with cardiomegaly in ACA from pulmonary trunk
- Histologically evident ischemic damage (acute or chronic) in 55%
  - 92% in ACA from pulmonary trunk

Lipsett, J, Cohle, SD, Berry, PJ, Byard, RW. Ped Path 1994; 14:287-300
COD or Incidental?

Factors associated with reduced flow in anomalous coronary arteries

- Ostial stenosis
- Ostial ridges
- Acute angle of arterial take-off
- Arterial hypoplasia
- External compression
- Intra-arterial compression
- Intramyocardial compression
- Intrinsic obliteratorive lesions

Lipsett, J, Cohle, SD, Berry, PJ, Byard, RW. *Ped Path* 1994; 14:287-300
Summing up

- Anomalies may exist in the face of normal origin and distribution of epicardial coronary arteries.
- Coronary ostia must be specifically identified and examined in all cases of sudden death.
- Must be familiar with protocols used by TPO contracted pathologists in assessing coronary arteries in such cases.
Coronary Artery Dissection

Case Report – SCD in a 39 year old female
Coronary Artery Dissection

Low power view of dissection

Histological detail of dissected LAD wall
Coronary Artery Dissection

- Female predominance
- Typically single vessel (LAD), short segment lesion within 2 cm of origin
- Histology
- Pathogenesis?
  - Role of hormones?
Primary Cardiomyopathies

- Dilated
- Hypertrophic
- Restrictive
Dilated
Cases 5 & 6

22-year-old female found dead in locked apartment by her father
Deceased 2 weeks post-partum
One previous pregnancy – healthy 2-year-old
Obese, 1 ppd smoker, H/O asthma, ?post-partum depression, no H/O substance abuse
Evaluate and discharged from ED for vague respiratory complaints 5 days PTD
Medications: escitalopram (Lexapro), albuterol, ibuprofen
Cases 5 & 6

- 67 inches, 254 pounds (BMI 39.8)
- 490 gm heart with biventricular dilation
- White foam in airways, 710/590 gm, no PE, no focal consolidation, diffuse congestion/edema
- Toxicology – escitalopram, caffeine, theobromine, nicotine, cotinine
Cases 5 & 6

- 32-year-old female found dead in bed
- Deceased 15 days post-partum, first pregnancy
- H/O ulcerative colitis, stable
- Labor induced at term for elevated liver enzymes
- Unremarkable post-partum course
Cases 5 & 6

- 68 inches, 151 pounds (BMI 23)
- Congested/edematous lungs (650/620 gm), no PE
- Toxicology negative
Cases 1 & 2

- 35 ml, clear, straw-colored pericardial effusion
- 430 gm heart with BVD, slight myxomatous changes of mitral valve
Histology

Case 5
► Diffuse, moderate myocyte hypertrophy
► Slight perivascular, no interstitial fibrosis
► Moderate fatty change RV with no inflammatory component
► Scout sections of nodal regions negative

Case 6
► Diffuse myocyte hypertrophy
► Perivascular and lacy interstitial fibrosis
► Focal fiber hypereosinophilia with smudged cross-striations
► RV with myocyte hypertrophy only
► Scout sections of nodal regions negative
Peripartum cardiomyopathy

- Relatively rare complication of late pregnancy and puerperium (1/3000-15000 LB)
- Diagnosed from one month before to five months after delivery
- High mortality, accounting for up to 4% of all maternal deaths annually – late dx a factor
- Recurrence in subsequent pregnancies of survivors has been reported
- Pathogenesis and potential risk factors are not well defined
Peripartum cardiomyopathy

- Persistent cardiomegaly beyond 6 months is a poor prognostic sign – 85% die of heart failure, surviving an average of 4.7 years.
- Those with persistent cardiomegaly are referred for transplant.
- Up to 50% have spontaneous resolution.
Peripartum cardiomyopathy

- Initial descriptions as far back as 1870
- Direct link with pregnancy first noted by Gouley in 1937
- Pathogenetic theories
  - Nutritional
  - Inflammatory (post-infectious/autoimmune)
  - Tocolytic therapy (induction or unmasking?)

Hypertrophic Cardiomyopathy
Familial Hypertrophic Cardiomyopathy

- Most common structural abnormality at autopsy in sudden death of young persons
- Autosomal dominant with variable penetrance and expression in 50-60%.
- Classically, asymmetrical septal hypertrophy with a bulge into the LVOT
- Most common presentation is sudden death
- Annual risk is 5-6% for children and 2-3% for adults
Familial Hypertrophic Cardiomyopathy
Familial Hypertrophic Cardiomyopathy

Dysplastic intramural coronary arteries
Familial Hypertrophic Cardiomyopathy

- Genetics
  - β-heavy chain myosin
  - Troponin T
  - Troponin I
  - Cardiac actin
  - α-tropomyosin and myosin binding protein C

- SCD incidence linked to the nature of the genetic mutation, not to the phenotypic expression
Restrictive

Endomyocardial fibroelastosis
Restrictive

Amyloid

Hemochromatosis
Don’t forget the right ventricle . . .

- 51-year-old female, substance abuse and bipolar disorder
- Relocated to NH from MA to be free of drug abuse environment
- Prescribed methadone in ER for back pain 6 days PTD
- Found dead in bed
- Pill count: “methadone taken as prescribed.”
Case 7 - Autopsy

- 68 inches, 232 pounds (BMI 35.3)
- Midline surgical scar over lumbosacral spine
- Right and left lungs 820 and 740 gm, patchy bilateral lower lobe consolidation
- 470 gm heart with biventricular dilation, thin, pale, yellow RV, no significant arteriosclerotic changes
- Toxicology: methadone 180 ng/mL, no EDDP, 7-aminoclonazepam 50 ng/mL
Case 8

- 28-year-old male research technician to matriculate to medical school in two months
- Long H/O “fainting spells” usually associated with exertion
- Wife occasionally auscultates – describes heart “racing, then skipping a beat then a ‘heavy beat’ before resumption of regular rhythm”
- Resting heart rate said to be ~42
- On no medications
Additional History

- Cardiac work-up in state just south of NH
  - EKG normal
  - Holter monitor – no significant abnormalities
  - Echocardiogram normal
- Competed in triathlon then joined friends for dinner, had 2 beers over 2 hours
- Upon leaving restaurant felt faint, laid on floor and had a seizure
- Failed 30 minute resuscitation attempt.
Autopsy

- 72 inches, 175 pounds
- Right and left lungs 880 and 830 grams with congestion and frothy edema
- 490 gm heart with marked dilation of RA/RV
  - No arteriosclerosis
  - Myocardium looks odd . . .
Histology

20X H&E

10X Trichrome
Arrhythmogenic Right Ventricular Dysplasia (ARVD)

- Clinically characterized by episodic V. tach., syncope and/or sudden death
- True incidence remains obscure
- Focal and segmental, making antemortem diagnosis elusive
- Progressive in some, static in others
ARVD

Pathogenetic theories

- Disontogenesis – 7 distinct chromosomal loci have been associated with ARVD (2 each on 10 and 14, 1 each on 1, 2 and 3)
- Degeneration
- Inflammation
- Apoptosis
- Environmental factors ??
- Currently thought to be a dystrophic myocyte disease that develops over time
## Proposed Diagnostic Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th><strong>Major</strong></th>
<th><strong>Minor</strong></th>
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<tbody>
<tr>
<td><strong>Global &amp;/or regional dysfunction and structural alterations</strong></td>
<td>Severe dilation and reduction of RV ejection fraction with no or mild LV involvement</td>
<td>Minor global RV dilation &amp;/or ejection fraction reduction with normal LV</td>
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<td>Localized RV aneurysms Severe segmental dilation of RV</td>
<td>Mild segmental dilation of RV Regional RV hypokinesia</td>
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<td><strong>ECG Repolarization abnormalities</strong></td>
<td>Epsilon waves or localized prolongation (110 ms) of the QRS complex in precordial leads (V₁-V₃)</td>
<td>Late potentials on signal averaged ECG</td>
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<tr>
<td><strong>ECG Depolarization/conduction abnormalities</strong></td>
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<td>LBBB type VT Frequent ventricular extrasystoles with LBBB morphology</td>
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<td><strong>Arrhythmias</strong></td>
<td>Familial disease confirmed at autopsy or surgery</td>
<td>Family H/O premature SCD (&lt;35)</td>
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<tr>
<td><strong>Family history</strong></td>
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Autopsy Findings

- Slight to no RV dilation
- Grossly evident fibrofatty replacement of RV free wall ± focal LV involvement
- “Triangle of dysplasia”
  - Pulmonary infundibulum
  - RV apex
  - Inferior RV wall
- Histology
  - Fibro-fatty with inflammation, focal myocyte necrosis
  - Fatty without inflammation (Caution advised)
Histology
Histology
Valvular heart disease

- Aortic stenosis
  - Congenital
  - Rheumatic
  - Calcific

- Mitral incompetence
  - Cause of death or incidental finding?
  - Histology
  - “Myxoid heart disease”
Valvular Heart Disease

- Hemodynamic stress
  - Stenosis
  - Regurgitation
  - Both

- Acute vs. chronic
- Acquired vs. congenital
- Susceptibility to infective endocarditis

Acquired stenosis of the aortic or mitral valve represents 2/3 of all valve disease
Rheumatic Heart Disease

- Pathogenesis
- Morphology
  - Acute
  - Chronic
Hemodynamic Consequences
Calcific Aortic Stenosis

- Morphology
- Clinical features
- Treatment
Myxomatous Degeneration of Mitral Valve
Myxomatous Degeneration of Mitral Valve

20 yo female with SCD
Endocardial friction lesion under posterior leaflet of mitral valve.

Cross-sectional view,
15 yo female, H/O syncope
Myxomatous Degeneration of Mitral Valve

- Myxomatous change found, to some degree in up to 5% of the population
- Prolapse *per se* is not likely the cause of death
- “Myxoid heart disease”
- Pathology
Infective Endocarditis
Infective Endocarditis
Infective Endocarditis
Case 9

- 21 year old male with sudden death
- 150 ml, straw-colored pericardial effusion
- 550 grams, LV 19 mm, RV 4 mm
- Epicardial hyperemia
- Mottled, focally hyperemic, soft, flabby myocardium
Histology
Myocarditis

- Etiology
  - Infectious
  - Drug hypersensitivity
  - Sarcoid
- Gross pathology
- Histology
- Organism-specific diagnosis
Myocarditis

- In the forensic setting most commonly infectious, drug hypersensitivity or sarcoid
- May present with a dilated, pale, flabby heart with focal epicardial &/or endocardial hemorrhage. . . or not.
- Antecedent illness hx common but not universal
- Cannot be recognized or excluded without histology
- Molecular biologic techniques allow organism-specific diagnoses.
Viral Myocarditis
**Case 10**

- 15-year-old male with arm and chest pain for 4 weeks, rx: naproxen
- CXR and “lab work” by PCP → Dx: pleurisy and B12 deficiency
- Increased SOB and “achiness” two nights PTD
- Went to bed at 23:30; “thud and moan” heard by parents at 23:55
- Found prone with agonal respirations and profuse sweating
- Failed aggressive resuscitative effort
Case 10

- ADHD treated with methylphenidate
- Member of school lacrosse team, but inactive recently due to arm and chest discomfort
- No known drug or alcohol use
- Mother has untreated septal defect dx’d as a child; no other family history of note
Autopsy

- 72 inches, 160 pounds
- Spleen with prominent white pulp
Autopsy

- Pulmonary congestion with frothy edema (650/490 grams)
- 115 ml pericardial effusion
- Heart 410 grams
Autopsy

The LVOT doesn’t look right . . .
Autopsy

But neither does the myocardium . . .
Giant Cell Myocarditis

20X

40X
Giant cell myocarditis

- Rare, frequently fatal (sudden cardiac death in >50%), no proven treatment
- Typically affects young, predominantly healthy adults
- Two presentations
  - Dilated cardiomyopathy with late deterioration
  - Rapid hemodynamic deterioration
- Transplant or death in 70% by one year after onset of symptoms
- Mechanism of death ventricular arrhythmia or refractory CHF
Giant cell myocarditis

- 19% associated with autoimmune disorders
  - Thymoma
  - IBD
  - Discoid lupus
  - Autoimmune hepatitis

- Drug-induced cases have been reported
  - NSAID
  - Antibacterials
  - Anticonvulsants
  - Anithypertensives (β-blockers)
Giant cell myocarditis

- Median transplant-free survival (N=30) without immunosuppression – 3 months (12.6 months with cyclosporin, a selective T-cell inhibitor, in combination with steroids, azathioprine or muromonad-CD3)
- 9/34 s/p transplant had recurrence in their transplanted heart, 1 died, 8 managed with augmented immunosuppression
- Overall post-transplant survival 71% at five years.
Giant cell myocarditis

- **Histology**
  - Widespread myocardial necrosis
  - Rich cellular infiltrate
    - Lymphocytes
    - Scattered eosinophils
    - Plasma cells
    - Macrophages
    - Multinucleated giant cells
  - Sarcoid is primary DDx
Giant cell myocarditis

IGCM

- Acute phase
  - Heavy mixed infiltrate, including macrophage-derived KP-1+ giant cells
  - Myocytic necrosis

- Healing phase
  - Granulation tissue
  - Moderate macrophagic giant cells

- Healed phase
  - Dense scar
  - No giant cells

Sarcoid

- Interstitial granulomatous disease
- No myocytic necrosis
- Multisystem distribution

Nodal Lesions

- Lipomatous hypertrophy of interatrial septum
- Cystic tumors of the AVN
- Hemorrhage into the conduction system
- Lev disease
- Calcification of the mitral annulus

- Collagen vascular
- Infiltrative diseases
- Dispersion of the AVN
- Congenital heart block
- AV nodal artery dysplasia
- Accessory conduction pathways
Cystic Tumors of the AVN

- Formerly dubbed “mesothelioma”
- IHC evidence suggests endodermal origin
- Strong female predominance
- Partial or complete heart block is the most common clinical presentation.
- Lesions partially or completely replace the AVN and rarely exceed 1 cm
Cystic Tumors of the AVN
AV Nodal Artery Dysplasia
Case 11

• 17-year-old female with sudden, witnessed arrest
• Social: athletic (swimming), no tobacco or drug use, occasional EtOH
• Hx: ADHD (Adderal), ear surgery, age 5
• Three siblings; 19, 15 and 13
• Observed by sister on couch, texting
• ~10 minutes later slumped on the couch, froth at mouth, sonorous respiration
• No history of chest pain, difficulty breathing, passing out, or seizure activity
Autopsy

- 70½ inches; 154 pounds
- Heart:
  - 368 grams
  - Coronary ostia normally placed and patent
  - Right predominant coronary artery system with no abnormality
  - Valves normal
  - Myocardium pale tan, soft and slightly flabby
  - LV 14 mm, RV 5
- Histology
  - Irregular myocyte hypertrophy
  - No perivascular or interstitial fibrosis
  - Nodal sections unremarkable
Laboratory and Follow-up

• Positive for mutation associated with LQTS
• Electrophysiological evaluation of other family members: mother and one sib with LQTS
The Channelopathies

- 350,000 sudden natural deaths per year in U.S.
- 4000 are under 35
  - Deaths between 15 and 34 increased 10% from 1989 to 1996
- 10-12% have no autopsy findings of significance
  - Up to 30% of autopsy negative SCD <15 are associated with pathogenic mutations
The Heart as an Electrical System

- Generation and transmission of electrical impulses
  - Specialized conduction tissue
  - Coordinated contraction of working myocardium
  - Orderly propagation of contractile wavefront
- Ventricular irritability (endogenous vs. exogenous)
Functional Aspects of Sudden Cardiac Death

- Transient acute electrical destabilization of myocardium
- Altered autonomic tone
- Altered electrolyte environment
- Coronary artery spasm
- Increased platelet adhesiveness
- Transient acute risk factors
- Predisposing chronic anatomic substrate

Ventricular tachyarrhythmia
LQTS

Rate corrected QT interval of > 0.46 sec\(^{1/2}\)

Prolonged repolarization of ventricles will degenerate to torsade d’ pointes (polymorphic ventricular tachycardia then ventricular fibrillation and death.)
Ion Channel Physiology

- Ion channels - a class of proteins that generate electrical signals
- Macromolecular protein tunnel spanning the lipid bilayer of the cell membrane
- Conformational change allows ion flow in or out of cell along electrical and chemical gradients
- Highly efficient - few in number
- Transmembrane potential is the sum of open vs. closed channels
Abnormal ion flow may prolong QT interval, degenerate to *torsade d’ pointes*, then v. fib.
The EKG tracing (left) is the manifestation of the cardiac action potential (right), which is in turn, a function of normally functioning ion channels.
Acquired
- Electrolyte imbalance, low K, Mg, Ca
- Decreased androgens (liver disease)
- Nutritional disturbances
- Intracranial disorders, incl. previous stroke
- Drug-related
Drugs and LQTS

- Amiodarone/Cordarone®
- Azithromycin/Zithromax®
- Bepridil/Vascor®
- Chloroquin/Aralen®
- Chlorpromazine/Thorazine®
- Citalopram/Celexa®
- Clarithromycin/Biaxin®
- Disopyramide/Norpace®
- Deftilide/Tikosyn®
- Dronedarone/Multaq®
- Droperidol/Insapine®
- Erythromycin
- Escitalopram/Lexapro®
- Flecainide/Tambocor®
Drugs and LQTS

- Halofantrine/Halfan®
- Haloperidol/Haldol®
- Ibutilide/Corvert®
- Moxifloxacin/Avelox®
- Ondansetron/Zofran®
- Pentamidine/NebuPent®
- Pimozide/Orap®
- Procainamide/Pronestyl®
- Quinidine/Quinaglute®
- Sevoflurane/Ulane®
- Sotalol/Betapace®
- Thioridazine/Mellaril®
- Vanetanib/Carelsa®
LQTS - Inherited

- Jervell & Lange-Nielson syndrome (AR)
- Romano-Ward syndrome (AD)
- Brugada Syndrome
- CVPT
- Other inherited cardiac conduction defects
- “Sudden unexpected nocturnal death syndrome”

- Syncope, seizures, sudden death
- 9% of children present with cardiac arrest
- 40% are asymptomatic at diagnosis
- 30% identified by screening first degree relatives after index case identified
- Ten year mortality 50% without treatment
Five most common genes implicated in autosomal dominant LQTS

- KVLQ1 (LQT1) 42%
- HERG (LQT2) 45%
- SCN5A (LQT3) 8%
- KCNE1 (LQT5) 3%
- KCNE2 (LQT6) 2%
>200 different mutations have been described in this group of genes

- Missense mutations: 72%
- Frameshift mutations: 10%
- In-frame deletions: 5-7%
- Nonsense mutations: 5-7%
- Splice-site mutations: 5-7%
Mutation Impact on Cardiac Action Potential

- LQT1; Chromosome 11 - Phase 3 potassium channel
- LQTS2; Chromosome 7 - Phase 3 potassium channel
- LQT3; Chromosome 3 - Phase 0 sodium channel
- Perturbed cardiac action potential prolongs QT interval
- Distinctive T-wave morphology?
Does Genotype Matter?

Frequency of cardiac events
- LQT1 63%
- LQT2 46%
- LQT3 18%

Death during cardiac event
- LQT3 20%
- LQT1 4%
- LQT2 4%
Current Status

- LQTS remains a clinical diagnosis
- Heterogeneity of LQTS mutations not yet fully defined
- Mutational frequency of LQTS not yet fully defined
- Genetic linkage analysis for large kindreds feasible
- Gene sequencing and definitive dx for individuals, sporadic cases and small kindreds not yet practical
Today’s Diagnostic Algorithm

Sudden, unexpected death
Non-natural etiology
Min. hx/gross autopsy neg
Histology reveals dx
Histology/toxicology neg
Toxicology yields dx
Re-evaluate

Diagnosis
Undetermined

Conduction system
Diagnosis
Undetermined

Molecular genetic screen
Heritable arrhythmogenic disorder
Undetermined
Diagnosis: LQTS; What next?

- Screen all first degree relatives of index case
- Symptomatic individuals *must* be treated
  - Beta-blocker therapy
  - Verapamil for those intolerant of above
  - Those with bradyarrhythmias - permanent pacemaker
  - Those with markedly prolonged QT interval (greater than 0.55 sec\(^{1/2}\)) - defibrillator implantation
- Asymptomatic individuals monitored closely with consideration of beta-blockers in those at higher risk
Clinical Vagaries

• Inheritance AD or AR?
• Variable penetrance
• Family testing recommended even when genetic testing is non-diagnostic
• One sodium channel gene is suspected in SIDS-type cases
Current SIDS theories

- Serotonin defect
- Defective immune response
- Metabolic, e.g. MCAD
- Cardiac arrhythmia syndromes – some studies claim up to 10%

NYOCME study

- SIDS: 10% with disease causing mutations
Commotio Cordis

- Instantaneous death following blunt impact of the chest
- Blow is received directly over the heart
- Diagnosis often rests entirely upon history
"Those who have dissected or inspected many bodies have at least learnt to doubt, while those who are ignorant of anatomy, and do not take the trouble to attend to it, are in no doubt at all." - Morgagni