Cardiac Toxicidromes

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Objectives

- Review effects of drugs of abuse on the cardiovascular system
- Case based approach to specific drugs including EtOH, cocaine, methamphetamine, inhalants
- Review digoxin toxicity and management
Case 1

38 yo male with hx heavy EtOH consumption for 15yrs
Homeless, living on street/shelters
Presents with fever, productive cough, dyspnea, RLL infiltrate
Admitted to GIM service
ECHO: EF < 15%, severe DCM, bicuspid aortic valve
Deteriorated on ward with increasing dyspnea, hypoxemia and hypotension
Afebrile, HR 130 sinus, BP 70/48, SpO2 84% on 15L
Brought to ICU lined, intubated, fluids pressors and inotropes initiated
Focused ECHO shows EF10%

How does EtOH affect the heart?
How do we manage this patient?
Alcoholic CM Pathophysiology

Not fully understood

1. EtOH induced apoptosis
2. Organelle dysfunction – mitochondrial structural changes, impaired Ca++ binding to sarcoplasmic reticulum
3. Acute and transient direct toxicity (acetaldehyde – impairs oxidative phosphorylation)
4. Nutritional deficiency (thiamine)
5. Chronic activation of RAS in EtOH abusers
Risk factors alcoholic CM

- Generally requires 80-90 g EtOH/day or 8-10 oz of hard liquor
- Genetic factors
  - ACE gene DD polymorphism linked to higher incidence of alcoholic cardiomyopathy
  - Other unrecognized factors
ALCOHOL

Alcohol consumption $\downarrow > 90\text{gms} > 5\text{ years}$

- Apoptosis (either directly via alcohol or indirectly via $\uparrow$ NE levels)
- $\downarrow$ synthesis and/or accelerated degradation of contractile proteins
- $\downarrow$ myofilament $\text{Ca}^{2+}$ sensitivity
- Intrinsic myocyte dysfunction due to mitochondrial and sarcoplasmic dysfunction (due to $\text{Ca}^{2+}$ overload, fatty ethyl esters or NE)

$\downarrow$

Cell drop out and weakly contracting myocytes

$\downarrow$

Decreased cardiac output

$\downarrow$

- LV dilation to increase EDV (preload) to compensate for $\downarrow$ cardiac output, however this is may be accompanied by wall thinning due to cell drop out
- Hypertrophy of normal myocytes to compensate for weakly contracting neighboring myocytes

Continued drinking $\downarrow > 15\text{ years}$

- Progressive LV dilation and wall thinning
- Activation of other neurohormonal systems
- Signs and symptoms of heart failure
Arrhythmias

- Can occur in up to 60% binge drinkers (holiday heart)
- Atrial fibrillation most common
- Ventricular – non-sustained VT
- Long QTc common in alcoholics
- Commonly have low Mg and K
Clinical presentation

- Acute or subacute onset LV failure
- Palpitations or syncope due to arrhythmias
- ECHO:
  - LV dilatation, increased LV mass, diastolic dysfunction
  - Systolic dysfunction often occurs later in course
- Endomyocardial bx – not usually necessary
- Labs – ↑ MCV, thrombocytopenia, ↑ GGT
Treatment – Acute ACM

- Hemodynamic stabilization, support of oxygenation and ventilation and symptom relief
- Invasive hemodynamic monitoring (art line and CVP +/- PAC)
- NIMV
- Intubation/mechanical ventilation + PEEP
- Vasodilators/diuretics if hypertensive
- Ultrafiltration
- Inotropic support – dobutamine, milrinone
- Mechanical support – IABP, LVAD
Treatment – chronic ACM

- Total and perpetual abstinence is goal
- Some evidence that cutting down to 20-60 g/d beneficial
- Standard therapy for CHF
  - ACE or ARB, BB, digoxin, diuretics are suggested
- Anticoagulation if EF <30% (caution – drunks tend to fall)
- Vitamin supplementation B12 and folate
Case 2

34 yo male presents with crushing RSCP, dyspnea, diaphoresis for past 1hr

Previously healthy, no famhx CAD

EtOH 3-4 beers/d, smoker 10pack yrs

“Occasional” crack cocaine use

Last used 2 hrs ago

HR 120  BP 190/118 RR 24 SpO2 94% RA
Any special considerations for treating this patient?
Cocaine
Cocaine

- Available as cocaine HCl (powder) and free base (crack)
- Smoked, inhaled, injected, ingested
- Onset < 1 min, peak 3-5 min, duration of action 30-60 min
- Most potent stimulant of natural origin
- Most common cause of acute drug related ED visits in N. America after EtOH
Cocaine - pharmacology

- Inhibition of neurogenic amine reuptake in synaptic cleft
- Also causes catecholamine release from central and peripheral stores
- Promotion of thrombus formation (activates platelets, stimulates thromboxane production)
- Na channel blockade – local anesthetic properties, prolongation of QRS and negative inotropy in large amounts
Cocaine ACS

1. Increase myocardial oxygen demand
   - ↑ chronotropy
   - ↑ inotropy
   - ↑ SVR

2. Coronary artery vasoconstriction and spasm
   - α – adrenergic stimulation

3. Coronary artery thrombus
   - Platelet stimulation/aggregation
   - Lower protein C and AT III levels

4. Accelerated atherosclerosis/endothelial damage – repeated episodes of HTN, coronary spasm
Clinical Characteristics in the Typical Patient With Cocaine -Induced Chest Pain

- Young age, usually less than 40 years
- Mostly males: 57-84%
- Smokers: 84 -91%
- Few other traditional cardiac risk factors
- Cocaine use within preceding 24 hours: 88%


Mittleman. Circulation, 1999;(21)2737
Diagnosis

- ECG often difficult to interpret as many users have LVH or early repolarization
- In one series 84% pts with cocaine CP had abnormal ECG
- ECG showing ischemia or infarction:
  - Sensitivity 36%
  - Specificity 90%
  - PPV 18%
  - NPV 96%
- Approximately 5-6% of pts presenting with chest pain associated with cocaine have MI

Treatment

- No placebo controlled RCTs regarding therapies to improve outcome
- Recommendations guided by animal studies, cath lab studies, observational studies and case reports
- Treatment should be similar to those with traditional ACS with a few notable exceptions
Treatment Recommendations (ACC/AHA Guidelines 2008)

- IV, O2(?), Monitor
- Benzodiazepines (I/B) - valium 5mg IV q3-5min or ativan 1-2 mg IV q5-10 min
- Aspirin (I/C)
- Nitroglycerin (I/B)
- Phentolamine (IIb/C) - 5-10mg IV q 5-15min
- Calcium channel blockers (IIb/C)
- PCI rather than fibrinolytics, when possible
β-blockers

- III/C - contraindicated
- Increase BP in setting of cocaine use
- Thought to be due to unopposed α-mediated vasoconstriction and coronary vasospasm
- Labetalol - no advantage over traditional β-blockers
  - Incr risk death in animal models
  - No reversal of vasoconstriction in humans
NaHCO₃

- QRS widening/VT rare, suggests profound toxicity
- NaHCO₃ 1-2 mEq/kg IV push
Cocaine-associated Chest Pain

ASA
Benzodiazepines

IV NTG, Nitroprusside for persistent Hypertension
(alternative: Phentolamine)

High Risk
STEMI
Primary PCI
Avoid B-blockers acutely
Antithrombotic and Antiplatelet therapy
(as indicated by existing guidelines)
Cardiac Catheterization

Low-moderate Risk
Observe in CPU
Drug Abuse Counseling
Stress Test Optional
Inpatient or Outpatient

NSSTE ACS
Discharge Therapy
ASA, clopidogrel, Statin, ACE I (as indicated by existing guidelines)
Consider B-blockers especially if high risk features (systolic dysfunction, dysrhythmia)
Drug Abuse Counseling
Cocaine – other cardiovascular sequelae

- Coronary artery aneurysm
- Myocarditis/cardiomyopathy
- Arrhythmias
- Stroke
- Aortic dissection

- Infective Endocarditis
  - can involve mitral or aortic valve
  - unusual organisms (Pseudomonas, Kebsiella, Candida)
Case 3

- 24 yo female brought in by “friends” from a party
- T 40°C  HR 140  BP 186/96  SpO₂ 98%  C/S 7.2
- GCS 13/15 –agitated, disheveled, clenching her jaw
- Friends mentioned she took several small pills and was “smoking some stuff”, but now they are nowhere to be found
- While IV being started she becomes severely agitated requiring 5 security guards to hold her down
- suffers a sudden cardiac arrest - resuscitation unsuccessful

What did she take?
Methamphetamine
Methamphetamine

- Crank, meth, speed, crystal or ice
- White or pale yellow powder that can be ingested, injected, snorted or smoked
- Displaces NE, DA, 5-HT from cytosolic vesicles and blocks reuptake
- Similar effects to cocaine, but peak effects in 2-3 hrs, longer duration of action (8-24 hrs)
Methamphetamine

- Euphoria, excitation, intensification of emotions, elevation of self esteem, increases alertness and aggression
- Tolerance to pleasurable effects occurs rapidly so user will continue to “tweak”
- Tachycardia and hypertension almost universal with acute intoxication
- Significant overdose causes severe sympathomimetic toxidrome and hyperthermia
Sudden cardiovascular collapse

- Cardiovascular collapse – particularly in agitated pt requiring restraint
- HTN, tachycardia, severely agitated delirium, hyperthermia, metabolic acidosis and seizures
- Cardiac arrest probably occurs due to combination of catecholamine depletion, acidosis, dehydration
- Treatment is supportive/preventive – fluids, BDZ
  - May require sedation, paralysis and active cooling
Methamphetamine Cardiac effects

- Acute MI, ischemia, cardiomyopathy in both acute and chronic users
- Toxic myocarditis with contraction band necrosis
Inhalants
Inhalants

- Organic solvents (cleaning products, fast drying glues, nail polish remover)
- Fuels (gasoline, kerosene)
- Propellants (freon, hydrofluorocarbons – hairspray, whipped cream)
- Pharmaceutical (ether, NO$_2$, amyl nitrate, butyl nitrate)
- In general – legal, cheap and readily available
Inhalants

Users tend to be people who have limited access to alcohol and other drugs
- Children, teenagers, incarcerated/institutionalized, marginalized individuals

- plastic bags - “bagging”
- solvent soaked rag - “huffing”
- directly from an open container - “sniffing”
- Canned air - “dusting”

- Produces euphoria, excitement, distortion in perception of time and space, hallucinations
- Side effects include H/A, N and V, intoxication
- May have “glue sniffers rash”
Toxic effects

- CNS manifestations caused by GABA agonist and NMDA antagonist effects
- Cardiac effects are thought to be due to sensitization of the myocardium to catecholamines
- Cruz et al (2003) demonstrated that toluene inhibition of voltage gated cardiac sodium channels may be a mechanism
Sudden Sniffing Death Syndrome

- Cardiac arrhythmia due to sensitization of myocardium to catecholamines
- Sudden alarm, attempting to flee, sexual activity
- Contributing factors:
  - Anoxia
  - Respiratory depression
  - Vagal inhibition and direct SA node depression
Supportive care with maintenance of airway, breathing and circulation

Arrhythmias should be treated with standard protocols
  - Avoid catecholamine infusions
  - Amiodarone seems to work best

Pay attention to electrolytes – toluene can cause type 1 RTA with hypokalemia, hypomagnesemia, hypocalcemia, and hyperchloremic metabolic acidosis

Cardiac arrest – no data to recommend deviation from standard ACLS management
Case 4

34 yo female, healthy, no meds

Ingested a herbal preparation marketed for “internal cleansing”

Ingredients not known to pt or listed in accompanying literature

Next morning developed nausea, vomiting and weakness

In ED BP 100/60 HR 30-40/min
Diagnosis?
Digitalis toxicity

- Cardiac glycoside available as digoxin, digitoxin
- Also found in plants: yellow oleander, foxglove, dogbane, lily of the valley, red squill
- Herbal dietary supplements
Digoxin - pharmacology

- Blocks Na\(^+\)-K\(^+\) exchange pump
- Increased intracellular Ca\(^{++}\) → Increased contractility
  - too much can cause ventricular ectopy, VT or VF
- Less negative resting membrane potential → incr automaticity
- Increased vagal tone
**Digoxin – Clinical Manifestations**

**Acute** – N & V, abdominal pain, lethargy, confusion, weakness

**Chronic** - Hallucinations, aberrations of color vision

**Cardiac Manifestations:**

- Combination of increased automaticity and depressed conduction
- Any dysrhythmia except rapidly conducted supraventricular tachycardias
- What 2 rhythms are relatively specific for cardiac glycoside toxicity?
  - Accelerated junctional rhythm and bidirectional VT
Digoxin -- Treatment

Airway/Breathing

- oxygen, secure airway, if necessary

Circulation

- **Atropine** may help reverse bradydysrhythmias if given early in acute toxicity

Decontamination

- Digoxin is rapidly absorbed

  - Multi-dose **activated charcoal** may be beneficial
Digoxin- Treatment

Digoxin-Specific Antibody Fragments

- Sheep derived antibody fragments
- Antibody complex is renally excreted
- Greater affinity for digoxin than the Na⁺ - K⁺ATPase
- Highly effective and safe!

Multicenter trial of 150 severely poisoned pts

- 50% chronic digoxin therapy
- 40% overdose with suicidal intent
- 10% inadvertent overdose
- 80% had complete resolution of signs/symptoms dig toxicity
- 46% mortality in those who had cardiac arrest

Antidote - Digibind

**Indications**
- Rhythm and conduction disturbances
  - Ventricular dysrhythmias
  - Bradydysrhythmias not responsive to atropine
- Serum K⁺ > 5.0 in an acute ingestion in an otherwise healthy person
- Serum digoxin level > 10ng/mL (12.8nmol/L) in an acute ingestion
- Ingestion of > 10 mg (4 mg in a child)

**Complications**
- Allergic reaction (rare)
- Withdrawal of digoxin effect (CHF, increased ventricular response rate, hypokalemia)
- Digoxin levels NOT meaningful after digibind
Digibind

Dosing of Digibind – give IV over 30 min unless cardiac arrest

Dose (vials) = \( \text{dig level ng/mL} \times \text{wt (kg)} \)

\[ \frac{100}{100} \]

Empiric dosing:

Acute OD = 10 vials

OR

If dose ingested is known:

\[ \# \text{ vials} = \text{amt ingested (mg)} \times 0.8 \]

\[ 0.6 \text{ mg/vial} \]
Consider Phenytoin, Lidocaine for suppression of ventricular automaticity without slowing AV conduction

**Ventricular Pacemakers**
- DO NOT delay digibind administration
- High rate of dysrhythmias

**Cardioversion and Defibrillation**
- Only if necessary for unstable rhythms
Digoxin - Treatment

Watch for and treat hyperkalemia—predictor of morbidity and mortality

Avoid Calcium?

“Stone Heart” phenomenon

Initial 2 cases described by Bower in 1939 – minimal data, both arrested after large dose of IV Calcium
Questions
Summary

DRUGS ARE BAD ... MMM KAY?
Other

? MARS for CCB

- Patient with severe diltiazem overdose hypotensive on 100mcg/min epi and norepi
- Off pressors within 6 hrs of initiation
MARS
The Ca++ “stone heart” controversy

“. . .in the presence of digitalis poisoning calcium may be disastrous, as intracellular hypercalcemia is already present.”

[Goldfrank’s Toxicologic Emergencies]

“. . .any extra calcium will cause such an intense contraction that the heart will never relax (this is called ‘stone heart’).”

[Introduction to Emergency Medicine]
THE ADDITIVE EFFECT OF CALCIUM AND DIGITALIS

A WARNING, WITH A REPORT OF TWO DEATHS

J. O. BOWER, M.D.
AND
H. A. K. MENGLE, M.D.

PHILADELPHIA
Prolonged plateau

Early afterdepolarization (arises from the plateau)

Calcium overload

Delayed afterdepolarization (arises from the resting potential)
32 yo F admitted with acute cholecystitis

Two days after surgery BP 90/50 and HR 100 with “extrasystoles” – digalen started

Day 6 post-op HR 120, “rapid and weak”

Two min after 10 cc IV Ca-gluconate she had a cardiopulmonary arrest

No reported K⁺ or Ca²⁺ levels
Bower’s 2\textsuperscript{nd} case

55 yo M w/ suspected hyperparathyroidism
- R thyroidectomy – no PTH tumor found
- Digalen “140 minims” given over 20 hrs [why?]
- Two days post-op he developed tremor
  “diagnosed as beginning tetany”
- Given Ca-chloride 10\% IV --- 50 cc’s !!
- “Cardiac collapse,” unable to resuscitate, no further info provided
Digitalis - Pharmacology

- Block Na⁺/K⁺-ATPase pump
- Increased intracellular Na⁺ reduces the driving force for the Na⁺/Ca²⁺ exchanger
- Ca²⁺ accumulates inside of cell
  - Increased inotropic effect
  - Too much intracellular Ca²⁺ can cause ventricular fibrillation, and possibly excessive actin-myosin contraction

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