Recreational (Illicit) Drugs and Cardiovascular Disease

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Case
• A 24 year old male presents to the hospital with about 1 month of worsening lower extremity swelling and shortness of breath
• He works as an independent tech contractor and his roommates are medical students
• An echocardiogram is performed and reveals severe left ventricular systolic dysfunction
• A comprehensive evaluation reveals no reason for cardiomyopathy
• IV diuretics and standard heart failure therapy is provided
• The day prior to discharge he admits to using methamphetamine so he can stay awake to work longer hours

Methamphetamine Chemistry
• Methamphetamine belongs to a class of compounds called phenylethylamines
• Phenylethylamines encompass a large group of biologically active compounds
  • Amphetamine, Dopamine, Ephedrine, MDMA, Bupropion, Ephedrine/Pseudoephedrine
• Ephedrine and Pseudoephedrine are likely the first discovered phenylethylamines
  • Extracted from Ephedra Sinica (ma huang)
  • Used in Chinese medicine for 5,000 yrs
  • Sympathomimetics used as stimulant, appetite suppressant, decongestant, vasoconstrictor, bronchodilator
  • Amphetamine and methamphetamine were developed in the late 1800’s as synthetic alternatives to ephedra

Modern Use Of Methamphetamine
• Amphetamine synthetic derivative of ephedrine developed in Germany 1887
  • Initially sold as Benzedrine as decongestant and bronchodilator
  • Stimulant effect of inhalers led to use in narcolepsy and for weight loss
  • Wide variety of uses: Schizophrenia, alcoholism, migraine, heart block, dysmenorrhea, persistent hiccups
• Amphetamine at 31 million prescriptions in 1967 (10 billion tablets made)
• Methamphetamine synthesized in crystallized form in 1920 Japan
  • Used by Germany in WWII as Pervitin tablets
  • Methedrine (methamphetamine tablets) introduced in 1940 for improvement of mood, energy, weight-loss
  • Vio inhalers available that contained 150-200mg methamphetamine
Rise of Recreational Methamphetamine Use

- Increased recreational use in the 1960s
- Limitations in prescription uses in the 1970s
- Motorcycle gangs continue illicit manufacture in the Pacific Northwest resulting in the moniker “crank” because it was hidden in crank cases
- Increased use in the 1980s by truck drivers and blue collar workers
- Importation of heated and inhaled “Ice” or “crystal” into Hawaii in the 1980s from the Phillipines
- Expansion of meth labs in the rural west
- Increased regulation to stop meth production in the mid 2000s


Street Names for Methamphetamine

<table>
<thead>
<tr>
<th>Street Name</th>
<th>Street Name</th>
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</thead>
<tbody>
<tr>
<td>Meth</td>
<td>Dimethedehydrinated methamphetamine</td>
</tr>
<tr>
<td>Sav MILL</td>
<td>Methbromine</td>
</tr>
<tr>
<td>Crystal meth</td>
<td>Methcynhine</td>
</tr>
</tbody>
</table>
| Hail        | Methchol
| Ice         | Methcol
| Sida         | Methanol
| Slate        | Methan
| Glass        | Methene
| Tin         | Methypine |
| Opiate       | Methypine
| Crystal      | Methypropine |
| Caffeine     | Methypropine |
| Red          | Methypropine |
| Blue         | Methypropine |
| Yellow       | Methypropine |

* One hit of “Tina” (1/4 gram) is about $25

Vearrier. Disease a Month, 2012.

Synthesis of (meth)amphetamine

Methamphetamine Laboratory Production
Simplified Methamphetamine Production “Shake and Bake”

Methamphetamine Use Is Pervasive Problem

- U.N. World Drug Report calls meth the most abused hard drug on earth
- 26 million meth addicts worldwide equals combined number for cocaine and heroin users
- Meth use cost the United States $23.4 billion in 2005


Methamphetamine Related Admission To Publicly Funded Substance Abuse Treatment Programs

- Evidence of growing methamphetamine use problem during the early 2000s
- Restrictions on sales of pseudoephedrine may have reduced access to methamphetamine
- Evidence suggests increasing global methamphetamine use


Methamphetamine Lab Incidents in 2004

Methamphetamine Use Has Migrated East During the Last Two Decades

Methamphetamine Use Has Remained Constant in the Last Decade

Methamphetamine Use Is Higher Among Certain Vulnerable Populations

- Men who have sex with men
  - Associated with high risk sexual behavior
  - Linked to increase in HIV transmission and other sexually transmitted infections
- Women
  - Equally common among men and women in contrast to other recreational drugs
  - Use initiated for depression and weight loss
  - Linked to domestic violence and sexual risky behavior
- Criminal Offenders
  - Associated with criminal and violent behaviors

Methamphetamine Is Commonly Used In San Francisco

<table>
<thead>
<tr>
<th>Population</th>
<th>Median Prevalence</th>
<th>Est. Pop. Size</th>
<th># of MA users</th>
</tr>
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<tbody>
<tr>
<td>MSM</td>
<td>13</td>
<td>34,000</td>
<td>7,000</td>
</tr>
<tr>
<td>MSM Iju</td>
<td>63</td>
<td>5,534</td>
<td>3,480</td>
</tr>
<tr>
<td>Male (EU)</td>
<td>42</td>
<td>3,075</td>
<td>2,971</td>
</tr>
<tr>
<td>Female (EU)</td>
<td>33</td>
<td>4,036</td>
<td>2,759</td>
</tr>
<tr>
<td>Youth (both male and female)</td>
<td>4.3%</td>
<td>62,494</td>
<td>2,781</td>
</tr>
<tr>
<td>Male Non-IDU / Non-MMM</td>
<td>3</td>
<td>207,428</td>
<td>65,271</td>
</tr>
<tr>
<td>Female Non-IDU</td>
<td>4</td>
<td>399,566</td>
<td>11,982</td>
</tr>
<tr>
<td>TG</td>
<td>71</td>
<td>1,186</td>
<td>445</td>
</tr>
<tr>
<td>TG-IDU</td>
<td>83</td>
<td>478</td>
<td>373</td>
</tr>
</tbody>
</table>

Pharmacokinetics Methamphetamine

- Route: PO, intranasal, inhaled (smoked), IV, PR
- Bioavailability
  - Oral 67%, inhalation 67-90%, nasal insufflations >79%
  - Onset of effect fastest with inhalation (5-10 seconds)
  - T1/2 = 12hr
- "High" can last 8-24hr
- Metabolism
  - Hepatic metabolism (CYP2D6)
  - Ethanol suppresses metabolism
  - Metabolites include amphetamine


Methamphetamine Pharmacology

- Redistributes monoamines from storage vesicles into synapses
- Inhibits metabolism of monoamines


Effects vary depending on dose, route, frequency of use

- Lower dose (5-50mg): euphoria, lowered inhibitions, decreased fatigue, acute improvement of attention, reduced appetite, mild-moderate tachycardia/hypertension
- Higher dose (>50mg): chest pain, tachypnea, tachycardia, HTN, diaphoresis, mydriasis, hyperthermia, hyperreflexia, agitation, delirium, psychosis, vasoconstriction (ischemia, CVA)
- Chronic high dose: cardiomyopathy, HF, PH, cognitive impairment, psychosis
- Cardiovascular effects strong correlation to dose


Methamphetamine Cardiac Clinical Pathology

- Acute pathology
  - Chest pain, tachycardia, HTN
  - Myocardial infarction
  - Aortic Dissection
  - SCD
- Chronic pathology
  - CAD
  - Cardiomyopathy (DCM)

Cardiovascular Findings On Autopsy of Meth Users in San Francisco

- Significant cardiomegaly (378g vs 341g)
- Coronary artery disease 79/413 versus 6/114 controls
- MI only identified in 1.8% (7/413)
- Myocardial fibrosis and contraction band necrosis
- No cardiomyopathy or pulmonary hypertension

Acute Coronary Syndromes and Methamphetamine

- Retrospective chart review from UC Davis
- 33 patients with methamphetamine and chest pain
- 9 patients diagnosed with ACS
- 3 patients found to have CAD on invasive evaluation
- Ventricular fibrillation ventricular tachycardia occurred in 2 patients

Cardiomyopathy Associated With Methamphetamine

- Few case reports of death associated with LV failure from 1940s-1970s
- First case of a living patient with cardiomyopathy from methamphetamine in 1989
  - 48 year old woman who used methamphetamine for weight loss, resolution with cessation of methamphetamine
- 3.4 fold higher odds of cardiomyopathy among patients who use meth

Histologic findings: Concentric hypertrophy, interstitial and perivascular fibrosis, myocyte vacuolization and medial hypertrophy

Possible Mechanisms Of Methamphetamine Cardiomyopathy

- Catecholamine excess
  - Vasospasm causing focal myocardial degeneration and necrosis
  - Similar to myocardial lesions in patients with pheochromocytoma or Takotsubo
- Increased reactive oxygen species and mitochondrial injury
- Direct toxicity that is independent of catecholamine mediated effects
  - Chronic meth has leads to degeneration of ultrastructure of cardiac myocytes
  - Beta-blockade does not prevent damage suggesting direct myotoxicity in addition to the toxicity from sympathetic overstimulation.
- Synergist effects with alcohol, cocaine

Kaye, Society for the study of addiction. 2007

CYP2D6 Polymorphisms May Predict Meth Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive metabolizer</td>
<td>2.33</td>
<td>0.54–10.13</td>
<td>0.257</td>
</tr>
<tr>
<td>Days of use</td>
<td>1.02</td>
<td>0.97–1.09</td>
<td>0.378</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.96–1.09</td>
<td>0.957</td>
</tr>
</tbody>
</table>

Sutter. Clinical Toxicology, 2013.

Methamphetamine and Heart Failure At SFGH

- Retrospective chart review of 199 patients with mod-severe/severe LV failure
- 123 Judged NICM, 23 (18.6%) Meth users
- Significantly younger (43 vs 54yrs, P<0.005)
- More hospital admissions (3.2 vs 0.8, P<0.005)
- Homeless (OR 6, 95% CI 1.6-22.5)
- Trend toward in-hospital death (OR 4.8, 95% CI 0.92-25.1)

Methamphetamine Has Been Associated With PAH and Increased Mortality

- Of 340, iPAH patients were more likely to be exposed (OR 11.6)
- Compared to iPAH, reduced 5 year survival (34% vs. 60%)

Methamphetamine Use in Patients with Idiopathic PAH At UCSF

- 56% (72/128) had history of meth use
- No difference in hemodynamics (mPAP, CO), 6MW, O2 use, age, or use of PDE-5, ERAs, inhaled prostacyclins or combination therapy
- Significant difference in survival for idiopathic PAH meth(+) versus idiopathic PAH meth(-)

Cocaine Is Derived From the Plant Erythroxylum coca

- Leaves chewed by South American Indians
- Cocaine isolated in the 1850s
- Used in “tonics” and original Coca Cola
- Variety of medical uses including an anesthetic and treatment of morphine addiction

Physiologic Actions of Cocaine

- Inhibits catecholamine reuptake at sympathetic nerve terminals
- Increases sensitivity or adrenergic receptors to norepinephrine
- Blocks Na+ and K+ channels (class I antiarrhythmic)
- Stimulates endothelin release
- Inhibits nitric oxide production
- Activates platelets and platelet aggregation

About 1.5 Million People Are Current Cocaine Users

Characteristics of Cocaine Users

Physiologic Consequences of Cocaine Use

Mechanisms of Action of Cocaine

Cocaine Chest Pain Is More Common Than MI From Cocaine

- Presenting with cardiovascular complaints 56%
- Presenting with chest pain 40%
- Presenting with myocardial infarction 6%
- Mortality 1%
Approximately 1 In 4 MI in Younger Persons Is Attributable to Cocaine

**Characteristics of Cocaine Chest Pain and MI**

- Chest pain onset as soon as 60 minutes or as long as 18 hours after use
- Risk of MI declines quickly after the first 4 hours
- Complications are rare >12 hours after arrival, usually present on arrival
- In patients with MI, non-obstructive disease with thrombus is a common finding
- Recurrent chest pain is common in persistent cocaine users

**Characteristics Cocaine Users With Stroke: ICH From Aneurysm Common In Current Cocaine Users**

- Odds of in hospital mortality and poor outcome 2.4

**Cocaine Cardiomyopathy**

- Dog and rabbit models develop cardiomyopathy after cocaine exposure
- Left ventricular dysfunction is common cocaine users undergoing angiography with EF <30% in 18% of patients
- 5.3% of patients with acute heart failure in the ADHERE-EM registry reported cocaine use
Aortic Dissection From Cocaine

- Incidence varies by center 0.5% -37% of aortic dissections
- Younger and more likely to be smokers
- No difference in presentation
- Thirty day mortality 10% higher in cocaine users


Suggested Algorithm for Treatment of Cocaine Chest Pain

Treatment of Meth and Cocaine Cardiomyopathy

- Abstinence
- Standard guideline directed heart failure therapy
- Unclear role of AICD given risk of ventricular arrhythmias