JUST SAY NO TO DRUGS?

THE EVIDENCE BEHIND MEDICATIONS USED IN CARDIAC RESUSCITATION

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CLASS CODE 148

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Objectives

1. Discuss the historical evidence supporting the use of Epinephrine, Vasopressin and Amiodorone in cardiac arrest.

2. Review recent publications evaluating the efficacy of Epinephrine, Vasopressin and Amiodorone.
2010 AHA ACLS Guidelines

- Bigger emphasis on compressions
- Early defibrillation
- Waveform Capnography
- Post resuscitation algorithm
- New guidelines in 2015
CPR Quality
- Push hard (≥2 inches [5 cm]) and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If PETCO₂ <10 mm Hg, attempt to improve CPR quality
- Intravascular pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Abrupt sustained increase in PETCO₂ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Shock Energy
- Biphasic: Manufacturer recommendation (120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- Monophasic: 360 J

Drug Therapy
- Epinephrine IV/IO Dose: 1 mg every 3-5 minutes
- Vasopressin IV/IO Dose: 40 units can replace first or second dose of epinephrine
- Amiodarone IV/IO Dose: First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway
- Supraglottic advanced airway or endotracheal intubation
- Waveform capnography to confirm and monitor ET tube placement
- 6-10 breaths per minute with continuous chest compressions

Reversible Causes
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-/hyperkalemia
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thrombosis, pulmonary
- Thrombosis, coronary
## Size of Treatment Effect

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Benefit &gt;&gt; Risk</td>
<td>Procedure/Treatment SHOULD be performed/administered</td>
</tr>
<tr>
<td>IIA</td>
<td>Benefit &gt;&gt; Risk Additional studies with focused objectives needed</td>
<td>IT IS REASONABLE to perform procedure/administer treatment</td>
</tr>
<tr>
<td>IIB</td>
<td>Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful</td>
<td>Procedure/Treatment MAY BE CONSIDERED</td>
</tr>
<tr>
<td>III</td>
<td>Risk ≥ Benefit No additional studies needed</td>
<td>Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL</td>
</tr>
</tbody>
</table>

### Level A
- Multiple (3-5) population risk strata evaluated
- General consistency of direction and magnitude of effect

### Level B
- Limited (2-3) population risk strata evaluated

### Level C
- Very limited (1-2) population risk strata evaluated

### Notes
- Suggested phrases for writing recommendations:
  - Recommend
  - Recommended
  - Recommended is indicated
  - Recommended is useful/effective/beneficial
  - Recommended is probably indicated or indicated
  - May/might be considered
  - May/might be reasonable
  - Usefulness/effectiveness is unknown/unclear/uncertain or not well established
  - May/might be considered
  - May/might be reasonable
  - Usefulness/effectiveness is unknown/unclear/uncertain or not well established
  - Not recommended
  - Not indicated
  - Should not
  - Is not useful/effective/beneficial
  - May/might be considered
  - May/might be reasonable
  - Usefulness/effectiveness is unknown/unclear/uncertain or not well established
  - Not recommended
  - Not indicated
  - Should not
  - Is not useful/effective/beneficial
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  - Not recommended
  - Not indicated
  - Should not
  - Is not useful/effective/beneficial

### Use of waveform capnography
- Perform CC while getting defib ready

### Placing the crash cart outside of the room to ward off evil spirits!

### Amiodorone & Epi
- LOE IIb/ A
Emergency medications – V-fib

- **Epinephrine** 1 mg every 3-5 min or
- **Vasopressin** 40 units instead of the 1st or 2nd Epi
- **Amiodorone**
  - 300 mg IV pulseless
  - 150 mg pulse

Circulation 2010, AHA ACLS Guidelines
Epinephrine

Current AHA guideline:
1 mg every 3 – 5 min in any pulseless rhythm
Rationale for use of Epinephrine

- Increased alpha 1 & alpha 2 effects
- Increased systemic vascular resistance
- Increased myocardial & cerebral blood flow
- Increased ROSC rates?  
- Increased survival to discharge?
Improved myocardial blood flow?

Decreased Cardiac Output with Epi

Cardiac Output L/min

<table>
<thead>
<tr>
<th>Time</th>
<th>Before Epi</th>
<th>After Epi</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 minutes</td>
<td>CPP 14 ± 4 mm Hg</td>
<td>CPP 29 ± 6 mmHg</td>
</tr>
<tr>
<td>4 minutes</td>
<td>P = &lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

Animal study evaluating CO in pigs

Improved cerebral blood flow?

- Animal study evaluating nine - 40 kg pigs
- Decreased microvascular perfusion with Epinephrine administration

Cerebral Blood Flow with Epi

Increases in CPP were not accompanied by increases in CBF

This persisted for over 3 min after Epi administration

Decreased microcirculatory flow with Epi?

- Reduced sublingual microcirculatory flow with ongoing CPR after Epi administration

Japanese EMS introduction of Epi

- Short term gain, but long term pain

- Increased ROSC rates, however,
  Decreased chance of survival at 1 month & decreased neurologic outcomes

N = 417,188

P < 0.001

All p = < 0.001

Hagihara et al (2012) JAMA

Japan EMS 2004 – Permitted to start IVs
2006 – Permitted to administer Epi
<table>
<thead>
<tr>
<th>Analysis</th>
<th>ROSC</th>
<th>1-Month Survival</th>
<th>CPC 1 or 2</th>
<th>OPC 1 or 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.91 (1.78-2.05)</td>
<td>0.71 (0.64-0.79)</td>
<td>0.41 (0.34-0.49)</td>
<td>0.43 (0.36-0.51)</td>
</tr>
<tr>
<td>Adjusted for propensity</td>
<td>2.01 (1.83-2.21)</td>
<td>0.71 (0.62-0.81)</td>
<td>0.41 (0.33-0.52)</td>
<td>0.43 (0.34-0.54)</td>
</tr>
<tr>
<td>Adjusted for propensity and selected variables</td>
<td>2.24 (2.03-2.48)</td>
<td>0.60 (0.49-0.74)</td>
<td>0.40 (0.26-0.63)</td>
<td>0.43 (0.28-0.66)</td>
</tr>
<tr>
<td>Adjusted for propensity and all covariates</td>
<td>2.51 (2.24-2.80)</td>
<td>0.54 (0.43-0.68)</td>
<td>0.21 (0.10-0.44)</td>
<td>0.23 (0.11-0.45)</td>
</tr>
</tbody>
</table>

Abbreviations: CPC, Cerebral Performance Category; OPC, Overall Performance Category; ROSC, return of spontaneous circulation.

For all odds ratios, P < .001.

Selected variables included age, sex, bystander eyewitness, relationship of bystander to patient, bystander chest compression, bystander rescue breathing, use of public-access automated external defibrillator by bystander, first documented rhythm, and time from call to arrival at the scene for the model with ROSC as a dependent variable. For other models, ROSC and the above selected variables were adjusted.

All covariates included all variables in Table 1 plus 46 dummy variables for the 47 prefectures in Japan for the model with ROSC as a dependent variable. For other models, ROSC, all variables in Table 1, and 46 dummy variables for the 47 prefectures in Japan were adjusted.
**VSE Study**  
Mentzelopoulos (2013) JAMA

- **RCT**
- **Vasopressin 20 IU + Epi 1mg q 3 min x 5 cycles + 40 mg Steroid - methylprednisolone (1st cycle)**

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Figure 2. Results on Survival Analysis

A) All patients

B) Patients with postresuscitation shock
Epinephrine in Cardiac Surgery Patients

- Look for causes!
  - Tamponade? Bleeding?
  - Resternotomy
- If primary V-fib, defibrillation x 3 sequential
- Do not give Epinephrine unless a senior provider advises to do so!
- *What’s the risk?*
  - Severe rebound hypertension leading to possible:
    - Aortic rupture
    - Suture line disruption

-Cardiac Surgery Advanced Life Support Guidelines
Epinephrine – What’s the evidence?

- **Alpha adrenergic effect**
  - Increase coronary & cerebral perfusion pressure (animal study - dogs)

- **No evidence linking to increased human survival**

- **Optimal dose? Who knows! NOT high dose!**
  - Possibly < 30 – 45 mcg/kg (< 2 – 3 mg)

- **Optimal interval? Who knows!**

- **High dose epi?**
  - 0.1 – 0.2 mg/kg (3 mg, 5 mg doses)

- **No difference in survival or neurologic outcomes**
  
  Paradis et al (1991) JAMA
  Brown et al (1992) NEJM
  Callaham et al (1992) JAMA
  Brown et al (1992) NEJM
  Steill et al (1992) NEJM
Ventricular fibrillation

- Most successful treatment for v-fib is defibrillation!
- For every minute delay, survival decreases by 10%!!!

N = 13,053
Amiodarone vs. Placebo
(after 3 successive shocks in OHCA)

Kudenchuk et al (1999) NEJM

N = 504
Amiodorone vs. Lidocaine

- OHCA
- Amiodorone superior to Lidocaine regardless of time administered

Note: Survival to hospital admission

Dorian et al (2002) NEJM
V-fib

**Amiodorone**

- 2 RCTs (OHCA) increased survival to hospital admission (vs. Lidocaine or placebo)
- Lacking evidence that it makes a difference in survival to discharge

Kudenchuk et al (1999) NEJM
Dorian et al (2002) NEJM

- For REFRACTORY V-fib, use **Amiodorone**
- 300 mg, may re-bolus with 150 mg
ALP Trial

- **Amiodorone** vs.
- **Lidocaine** vs.
- **Placebo**

- Out of hospital v-fib arrest

- Goal is drug administration < 10 minutes after arrival on scene

- Resuscitation Outcome Consortium (ROC) study group

- Multi-city EMS trial

- Still enrolling patients

- Goal: 3,000 patients
Torsades de Pointes

- Magnesium!!!
- Effective for termination of Torsades de Pointes associated with prolonged QT

**Empiric dosing with Magnesium is not shown to be beneficial for in-hospital cardiac arrest**


Perticone et al (1986) AMJ
Gone by the wayside?

- What happened to Lidocaine???!!!
  **Amiodorone was superior**

- What happened to Magnesium???!!!
  **No benefit, except in Torsades de Pointes**

- What happened to Calcium Chloride
  **No benefit**
PEA – Pulseless Electrical Activity & Asystole

- **Pump**
  - at least 100 cpm
  - 2 inch depth

- **Epi**
  - 1 mg Q 3 – 5 min

- **Assess**
  - the causes

- Atropine?
  - No longer recommended
  - Initial use was based on a case study of 8 patients

References:
Symptomatic bradycardia

- **Atropine** 0.5 mg up to 3 mg
  - removed from algorithm (except in symptomatic bradycardia)
  - Do not give if the cause is heart block secondary to MI or any quickly reversible cause
  - Doses < 0.5 mg may cause paradoxical bradycardia

- 2nd line (not responsive to atropine):
  - Pacing
  - Dopamine infusion 5 – 20 mcg/kg/min or
  - Epinephrine infusion – 2 – 10 mcg/min
When is Bicarb appropriate?

- Hyperkalemia
- Acidosis that was bicarb responsive pre-arrest
- Tricyclic antidepressant overdose

- Not JUST BECAUSE!!!
Route of administration

- Abandoned endotracheal administration
  - Not effective
- Whatever route does not interrupt chest compressions!
- IV
- IO
Intra-osseous access
Summary on drugs...

- Some have demonstrated increased ROSC
- None have shown long term benefit in RCT
- Most studies are based on OHCA
- Lower doses of Epi are likely better than higher doses (> 5 mg)
- Amiodarone is better than Lidocaine, but no survival benefit
- Don’t give bicarb just because...
In conclusion…

- The focus of cardiac resuscitation should be on high quality CPR, minimal interruptions
- Defibrillate early, minimize pre/post shock pauses
- Incorporate waveform Capnography
- Less emphasis on medications
- Control the temperature post arrest

- Code 148