Management of Refractory Ventricular Fibrillation

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Pharmacy Grand Rounds
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Patient Case

Code 45 Response

• AB is a 30 year old male POD#3 from aortic root and valve replacement

• Received 2 defibrillations and 1 mg of epinephrine
• iSTAT in progress
Is AB in refractory ventricular fibrillation?

- A. Yes
- B. No
Objectives

• Define refractory ventricular fibrillation
• Compare different antiarrhythmic agents for the management of refractory ventricular fibrillation
• Examine emerging strategies for the management of refractory ventricular fibrillation
Etiology

- Myocardial ischemia
- Electrolyte disturbances
- QT prolongation
- Drug toxicity
When Does it Become Refractory?

• Early definitions
  • Failure to respond to first line therapy
  • Failure to terminate after five defibrillations
  • Dependent upon ICD placement

• AHA 2017 guideline:
  • Cardiac instability defined by ≥3 episodes of sustained VT, VF or appropriate ICD shocks within 24 hours
Which drug do you recommend next?

- A. Amiodarone
- B. Lidocaine
- C. Procainamide
- D. Bretylium
Advanced Cardiac Life Support

VF/VT?
- Defibrillate
- CPR 2 minutes

VF/VT
- Defibrillate
- CPR 2 minutes
- *Epinephrine q3-5 min*

VF/VT
- Defibrillate
- Amiodarone 300 mg
- Lidocaine 1.5 mg/kg if unavailable
- CPR 2 minutes
Choice of Antiarrhythmic
Amiodarone

1999
- ARREST
- 500 patients randomized, double-blind study of 300 mg amio IV to placebo in out-of-hospital cardiac arrest
- Amio group more likely to achieve ROSC

2002
- ALIVE
- 347 patients randomized to 1.5 mg/kg lidocaine or 5 mg/kg amiodarone after out-of-hospital cardiac arrest
- Amio group more likely to survive to hospital admission

2016: ALPS
Amiodarone 300 mg
Lidocaine 120 mg
Placebo

Kudenchuk PJ et al. NEJM 1999
Dorien et al. NEJM 2002
Kudenchuk PJ et al. NEJM 2016
### Amiodarone, Lidocaine or Placebo Study

**Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Amiodarone (n=974)</th>
<th>Lidocaine (n=993)</th>
<th>Placebo (n=1059)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSC</td>
<td>35.9%</td>
<td>39.9%</td>
<td>34.6%</td>
<td>0.52</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>45.7%</td>
<td>47%</td>
<td>39.7%</td>
<td>0.01</td>
</tr>
<tr>
<td>Survival to discharge</td>
<td>24.4%</td>
<td>23.7%</td>
<td>21%</td>
<td>0.08</td>
</tr>
<tr>
<td>mRS ≤ 3</td>
<td>18.8%</td>
<td>17.5%</td>
<td>16.6%</td>
<td>0.19</td>
</tr>
</tbody>
</table>

mRS = modified Rankin score
ROSC = return of spontaneous circulation

Kudenchuk PJ et al. NEJM 2016
Amiodarone or Lidocaine

Takeaways

• Both amiodarone and lidocaine showed similar benefits in short-term outcomes
  • Increase in survival to hospital admission vs placebo

• Neither improved survival to hospital discharge
  • Poor neurologic outcomes
  • Median mRS of 5
AB

Ongoing chest compressions

3 defibrillations

3 mg epinephrine

300 mg amiodarone

200 mg lidocaine
Is There a Role for Procainamide?

PROCAMIO

Stable VT

Procainamide 10 mg/kg (n=33)
- 9% cardiac events
- 67% termination of VT

Amiodarone 5 mg/kg (n=29)
- 41% cardiac events
- 38% termination of VT

Ortiz et al. Eur Heart J 2016
What About Procainamide?
Role In Out of Hospital Arrest

VT/VF

Procainamide eligibility

176 received procainamide
- 45% admitted to hospital
- 18% discharged

489 did not receive procainamide
- 62% admitted to hospital
- 32% discharged

Markel et al. Acad Emerg Med 2010
## Antiarrhythmic Agents
### Other agents

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Trials</th>
<th>Pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bretylium</td>
<td>Inhibits NE release, K⁺ channel blocker</td>
<td>Burn et al 1964 Chandrasekaran 1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Discontinued</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>Blockade of frequency dependent Na⁺ channels</td>
<td>RAID 2018</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Studied as primary prevention in patients with ICD and not found to have benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drug of choice in Brugada syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Congenital short QT syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• *Increased risk of mortality in post-MI patients</td>
</tr>
<tr>
<td>AB</td>
<td></td>
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</tr>
<tr>
<td>------------------</td>
<td>-----------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Ongoing chest</td>
<td>compression</td>
<td></td>
</tr>
<tr>
<td>14 defibrillations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 mg epinephrine</td>
<td></td>
<td></td>
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<tr>
<td>600 mg amiodarone</td>
<td></td>
<td></td>
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Magnesium

For patients with recurrent TdP, intravenous Mg is recommended

12 consecutive patients with TdP

9/12 TdP patients aborted with 2 g Mg

5 VF patients did not abort

In patients with VF not related to TdP, administration of Mg is not beneficial

RCT of refractory VF patients (>3 shocks)

No difference in ROSC (17% vs 13%) or Survival (4% vs. 2%)

*marked hypokalemia may be an indication to replace magnesium
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<tr>
<td>Magnesium 4 g IV</td>
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Poll everywhere

• Which intervention would you consider to be most likely to benefit AB?
  • A. Esmolol
  • B. Stellate Ganglion Block
  • C. Isoproterenol
  • D. Extracorporeal Membrane Oxygenation
**AB**

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Epinephrine in Cardiac Arrest – Harmful?

• Increases myocardial oxygen demand
  • Primarily through activation of beta-1 receptors
  • Leads to worsening ischemic injury
    • Subsequent increases in cAMP lead to excess Ca^{2+} concentrations in cardiocyte
    • Free radicals as byproducts of catecholamine degradation contribute to myocardial injury
  • *Lowers VF threshold*

Beta Blockade – Just a theory?
Dogs in Ventricular Fibrillation

22 dogs induced into cardiac arrest

Control (n=11)
6/11 dogs successfully defibrillated

Propranolol (n=11)
9/11 dogs successfully defibrillated

Ditchey RV et al. J Am Coll Cardiol. 1994
Beta Blockade

Early Results Takeaways

• Animal data suggests potential benefit from *pretreatment* with beta blockade

• Early case reports describe termination of refractory VF with intravenous propranolol
  • Refractory definitions vary
  • Unclear role of other antiarrhythmics in these cases

• Early 1990’s practice recommendations published in the Journal of Critical Illness and by the AHA recommend 1 mg/min propranolol IV
Beta Blockade
Is There Still a Benefit?

VT/VF

ACLS Protocol (n=22)
- Lidocaine 1 mg/kg → Continuous infusion
- Procainamide 100 mg q5 minutes

Sympathetic Blockade (n=27)
- Propranolol (n=14)
- Esmolol (n=6)
- Ganglion Block (n=6)

Nademanee K et al. Circulation 2000
ACLS vs. Sympathetic Blockade

Results

ACLS

4/22 patients survived

18 expired (all VF)

Sympathetic Blockade

21/47 patients survived

6 expired (3 VF)

Nademanee K et al. Circulation 2000
Beta Blockade
Is there enough evidence to recommend?

<table>
<thead>
<tr>
<th>Study design</th>
<th>Patient s</th>
<th>Population</th>
<th>Intervention</th>
<th>Results</th>
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<tbody>
<tr>
<td>Miwa et al</td>
<td>Prospective, observational</td>
<td>42</td>
<td>Electrical storm refractory to class III agents</td>
<td>Landiolol</td>
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<tr>
<td>Driver et al</td>
<td>Retrospective observational</td>
<td>25</td>
<td>Out of hospital arrest with RVF</td>
<td>Esmolol</td>
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<tr>
<td>Lee et al</td>
<td>Retrospective, pre/post protocol</td>
<td>41</td>
<td>Out of hospital arrest with RVF</td>
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AHA 2017 Guidelines:
In patients with a recent MI who have VT/VF storm, an intravenous beta blocker can be useful (IIa, B-NR)
AB

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**Esmolol 500 mcg**
Beta Blockade
Stellate Ganglion Block

• Stellate ganglion is a group of nerves located at the base of the neck
  • Controls sympathetic function
• Block can be achieved with targeted injection of local anesthetic
  • Lidocaine, xylocaine, bupivacaine
• Not currently included in AHA guidelines
Stellate Ganglion Block

Evidence

- Many case reports of termination of electrical storm after ganglion block
- 2017 review found 38 patients from 23 studies
  - Most commonly mixed VT/VF
  - Precipitating causes were MI or prolonged QT
  - Bupivacaine most commonly utilized
  - Decreased VA burden from 12 to 1 episode/day
  - 80% of patients survived to discharge
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Overdrive pacing
Is Beta Activity Always Harmful?

- AHA Guidelines:
  - In patients with recurrent TdP associated with acquired QT prolongation and bradycardia, increasing heart rate with pacing or isoproterenol are recommended (I, B-NR)
Overdrive Pacing

Isoproterenol

• Potent $\beta_1$ and $\beta_2$ agonist

• Subsequent increase in heart rate can shorten QT interval and effective refractory period
  • Contraindicated in congenital long QT syndrome

• Multiple case reports describe termination of TdP with isoproterenol administration
  • Likely most useful as a bridge to transvenous pacing

• One case report describes reversal of RVF in an adult patient with apparent short QT syndrome
  • Limited other options for treatment

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Extracorporeal CPR

Background

• Extracorporeal Membrane Oxygenation (ECMO) has been utilized during CPR as a bridge to definitive treatment
  • Referred to as ECPR

• Animal models demonstrate efficacy of ECPR
  • Pigs with occluded LAD and refractory VF cannulated after 45 minutes of resuscitation
  • 60% able to achieve ROSC after revascularization

Debaty et al. Resuscitation 2017
Sideris G et al. Resuscitation 2014
ECPR

Does it improve outcomes?

- Case series vary in mortality/morbidity rates
  - Little data in North American population
- Extracorporeal Life Support Organization (ELSO) keeps prospective database of cases

![Survival and Cannulation Time Graphs]

Survival

- ECMO: 30%
- OHCA 2016: 10%
- IHCA 2016: 20%

Cannulation Time

- Survival: 30
- Non-survival: 60
ECPR

SAVE-J Trial

VF/VT

- 26 ECPR hospitals: 13.7% favorable neurologic outcome
- 20 non-ECPR hospitals: 1.9% favorable neurologic outcome

Sakamoto T et al. Resuscitation 2014
Ongoing chest compressions
35 defibrillations
14 mg epinephrine
600 mg amiodarone
200 mg lidocaine
1 g procainamide
Magnesium 20 g IV
Esmolol 500 mcg
Stellate Ganglion Block

ECPR
Future directions

• In hospital cardiac arrest
• In hospital ECPR
• Continuous infusions
• Combination therapy
Management of Refractory Ventricular Fibrillation

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