A Cure for the Code Blues?
Vasopressin, Steroid and Epinephrine Cocktail for Use in Advanced Cardiac Life Support

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August 28, 2015

Learning Objectives

1. Define therapeutic endpoints for basic life support and advanced cardiac life support (ACLS)
2. Describe the current level of evidence for vasopressor agents recommended by national ACLS guidelines
3. Identify complications following return of spontaneous circulation which may decrease survival
4. Analyze evidence for role of combination vasopressin, steroids and epinephrine in ACLS
I. Cardiac arrest (CA)

Figure 1. Introduction to CA

A. Incidence
   i. Out-of-hospital cardiac arrests (OHCA): 94 per year per 100,000 people
   ii. In-hospital cardiac arrests (IHCA): 1-5 per 1,000 patient admissions
      a. Bias due to lack of official reporting and documenting

B. Survival rates
   i. Favorable determinants
      a. Younger age
      b. Fewer comorbidities
      c. Ventricular fibrillation (VFib) or pulseless ventricular tachycardia (VTach)
      d. Witnessed arrest
      e. Shorter time to chest compressions and defibrillation
      f. Shorter duration of code
      g. IHCA
      h. Occurrence during the day on a weekday
   ii. National OHCA survival to hospital discharge: 3-16%
   iii. National IHCA survival to hospital discharge: 23%
      a. VFib or VTach: 18-64%
      b. Pulseless electrical activity (PEA) or asystole arrests: 1-14%
   iv. 60% of patients do not survive to discharge after return of spontaneous circulation (ROSC)
      a. Most deaths following ROSC occur within 24 hours
   v. Neurologic function
      a. Severe cerebral disability or vegetative state in 25-50%
      b. Post-cardiac arrest brain injury manifests as coma, seizures, myoclonus, neurocognitive dysfunction and brain death
      c. Contributory factors: microcirculatory failure, impaired cerebral autoregulation, hypercarbia, hyper/hypoxia, pyrexia, hyperglycemia and seizures
C. Pathophysiology of CA

i. Lack of effective cardiac contraction with minimal cardiac output (CO)

ii. Presenting rhythms
   a. Shockable
      1. VTach – organized electrical activity of ventricles
      2. VFib – disorganized electrical activity of ventricles
   b. Non-shockable
      1. PEA – additional rhythms with lack of sufficient ventricular activity to generate pulse
      2. Asystole – absence of detectable ventricular electrical activity
         aa. End-stage rhythm following prolonged VFib or PEA
         ab. Worst prognosis

iii. Etiology
   a. Underlying cause
      1. Non-reversible causes
      2. Reversible causes, “H’s and T’s” (see Appendix A)

iv. Physiologic response
   a. Activation of sympathetic nervous system
      1. Increases plasma catecholamines
      2. Releases vasopressin (VASO) and activates renin-angiotensin-aldosterone system
   b. Hypothalamic-pituitary-adrenal (HPA) axis response

Figure 2. HPA axis

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II. Basic Life Support (BLS) and Advanced Cardiac Life Support (ACLS)

A. Guidelines

i. American Heart Association (AHA) ACLS 2010

ii. European Resuscitation Council (ERC) 2010

Figure 3. Chest compressions

A. Defibrillation

i. VFib or VTach rhythms following every cycle of chest compressions
   a. Biphasic preferred, initial 120-200 J
   b. Increases survival

B. Ventilation

i. Bag-mask-valve with 100% FiO2
   a. 2 breaths every 30 seconds without advanced airway
   b. 1 breath every 6-8 seconds with advanced airway

ii. Minimize excessive ventilation
   a. Increases intrathoracic pressure, decreases blood flow to vital organs
   b. Other complications: gastric inflation, regurgitation, aspiration

C. Medications in ACLS

i. Administered by intravenous (IV) or intraosseous (IO) route

ii. Increase cardiac and cerebral perfusion pressure

iii. Facilitate restoration and maintenance of a perfusing spontaneous rhythm

iv. Guideline recommended drug therapy (See Appendix B)

   a. All rhythms
      1. Epinephrine (EPI)
      2. VASO

   b. Refractory VFib/VTach
      1. Amiodarone
         aa. α, β, Na⁺, K⁺, Ca²⁺ channel antagonist
         ab. After 1° defibrillation attempt, following 2 minutes of chest compressions
         ac. Increases ROSC and survival to hospital admission
v. Clinically evaluated endpoints
   a. ROSC
   b. Short term survival/survival to hospital admission
   c. Survival to hospital discharge
   d. Survival to hospital discharge with favorable neurologic recovery
      1. Cerebral Performance Category (CPC) (See Appendix C)
   e. Long term survival
vi. Evidence for medications
   a. Increase ROSC and survival to hospital admission when compared to no medications
   b. Every 1 minute delay in vasopressor administration is a 4% decrease in ROSC
   c. None for long-term survival or favorable neurologic outcomes
vii. Consider reversible causes and treat underlying pathophysiology (See Appendix A)

II. EPI

A. Background\textsuperscript{13,16}
   i. Catecholamine hormone and neurotransmitter
   ii. Chemical mediator conveying nerve impulses to organs (heart, lung, etc.)
   iii. First used in 1906 to treat CA
   iv. Integral part of CPR recommendations since 1974

Figure 4. EPI plasma concentrations\textsuperscript{10}

![EPI plasma concentrations graph]

B. Dosing\textsuperscript{8}
   i. 1 mg every 3-5 minutes IV/IO

C. Mechanism of action\textsuperscript{8,12,17,19-24}
   i. \(\alpha\)- and \(\beta\)-adrenergic receptor stimulation
   ii. \(\alpha_{1}/\alpha_{2}\) - vasoconstriction
      a. Most potent catecholamine for \(\alpha\) stimulation
      b. Increases coronary and cerebral perfusion pressures
         1. Increases ROSC
      c. Decreases microcirculatory cerebral blood flow
         1. Increases severity of cerebral ischemia during CPR
         2. Impairs neurologic function
iii. \( \beta_1 \) - inotropic, chronotropic
    a. No evidence of benefit from \( \beta \)-stimulation
       1. \( \beta \)-agonism has demonstrated harm over BLS alone
       2. Decreases survival vs. phenylephrine or EPI + esmolol
       3. Increases defibrillation attempts required to attain ROSC
    b. Detrimental effects
       1. Increases myocardial work, oxygen consumption and utilization of scarce energy reserves
          aa. Lactic acid production
          ab. Ectopic ventricular arrhythmias
          ac. Secondary VFib
       2. Transient hypoxemia due to pulmonary arteriovenous shunting
       3. Post-ROSC tachycardia and hypertension
          aa. Precipitates recurrence of VFib
       4. Post-cardiac arrest myocardial dysfunction
          aa. Greater incidence of post-resuscitation shock

iv. \( \beta_2 \) - vasodilation
    a. Increases blood flow to skeletal muscles
    b. Predominantly masked by \( \alpha_1 \) effects

D. Efficacy data

<table>
<thead>
<tr>
<th>Author</th>
<th>((n))</th>
<th>Patients</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
</table>
| Woodhouse et al. 1995   | 339    | OHCA/IHCA Asystole or resistant VFib | Prospective RCT  
HDE= 10 mg x 2 vs.  
SDE= 1 mg x 2 or placebo (not randomized) x 2  
Followed by open label 1 mg EPI | No difference in: Immediate survival  
Hospital discharge |
| Herlitz et al. 1995     | 1203   | OHCA VFib              | Retrospective  
EPI after ≥3 rounds defibrillation vs. no EPI regardless of defibrillation attempts | ↑ ROSC  
↑ hospital admission  
No difference in: Hospital discharge |
| Ong et al. 2007         | 1296   | OHCA                     | Prospective observational  
Before vs. after protocol:  
EPI 1 mg x 1 prior to transport with 1 mg dose x 1 in ED | No difference in:  
ROSC  
Hospital admission  
Hospital discharge |
| Olsveengen et al. 2010  | 851    | OHCA                     | Prospective RCT  
ACLS with vs. without IV access and standard drugs | ↑ ROSC  
↑ hospital admission  
↑ CPR time  
No difference in: Hospital discharge  
Favorable neurologic outcome |
| Jacobs et al. 2011      | 534    | OHCA                     | Prospective, DB, RCT  
EPI 1 mg vs. placebo every 3 min | ↑ ROSC  
↑ hospital admission  
No difference in: Hospital discharge |

*All differences demonstrated statistical significance

OHCA: out-of-hospital cardiac arrest; IHCA: in-hospital cardiac arrest; RCT: randomized controlled trial; HDE: high dose epinephrine; SDE: standard dose epinephrine; EPI: epinephrine; VFib: ventricular fibrillation; ROSC: return of spontaneous circulation; ED: emergency department; ACLS: advanced cardiac life support; IV: intravenous; CPR: cardiopulmonary resuscitation; DB: double blind
E. Bottom line  
   i. EPI increases likelihood of achieving ROSC and survival to hospital admission  
   ii. Effects on long-term survival remain uncertain  
   iii. No role for higher doses  
      a. No improvement in survival with EPI doses > 1 mg  
   iv. Dose-dependent adverse effects  
      a. Unfavorable neurologic outcomes  

III. VASO  
A. Background  
   i. Endogenous peptide and antidiuretic hormone  
   ii. Regulates water retention and electrolyte homeostasis  
   iii. Increases peripheral vascular resistance  
   iv. Guideline recommendations  
      a. AHA: alternative to EPI since 2000  
      b. ERC: not enough evidence to recommend or refute use  

Figure 5. VASO plasma concentrations  

B. Dosing  
   i. 40 units once IV/IO  
      a. May replace first or second dose of EPI  

C. Mechanism of action  
   i. Non-adrenergic peripheral vasoconstrictor  
      a. Stimulates smooth muscle \( V_1 \) receptors  

D. Physiologic effects  
   i. Increases coronary perfusion pressure  
   ii. Causes cerebral vasodilation  
   iii. Minimal effect on pulmonary vasculature  
   iv. Longer \( t_{1/2} \) and duration of effect than EPI  
      a. Increases mean arterial pressure (MAP) post-resuscitation  
   v. Potentiates release of ACTH and cortisol  
   vi. Greater stability in acidic environment compared to catecholamines
E. Efficacy data

<table>
<thead>
<tr>
<th>Author</th>
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<th>Results</th>
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<tbody>
<tr>
<td>Linder et al. 1997</td>
<td>40</td>
<td>OHCA Resistant VFib</td>
<td>Prospective, DB, RCT, VASO 40 units x 1 vs. EPI 1 mg x 1 Followed by standard ACLS medication</td>
<td>↑ ROSC ↑ hospital admission ↑ 24 hr survival No difference in: Hospital discharge Good neurological outcome</td>
</tr>
<tr>
<td>Stüell et al. 2001</td>
<td>200</td>
<td>IHCA</td>
<td>Prospective, RCT, triple blind VASO 40 units x 1 vs. EPI 1 mg x 1 Followed by open label EPI</td>
<td>No difference in: ROSC Hospital discharge Neurologic outcome Survival</td>
</tr>
<tr>
<td>Wenzel et al. 2004</td>
<td>1186</td>
<td>OHCA</td>
<td>Prospective MC, DB, RCT VASO 40 units every 3 min x 2 vs. EPI 1 mg every 3 min x 2 Followed by open label EPI</td>
<td>(↑ hospital admission, ↑ hospital discharge in asystolic patients) No difference in: Hospital admission Hospital discharge Cerebral performance</td>
</tr>
<tr>
<td>Grmec et al. 2005</td>
<td>109</td>
<td>OHCA VFib/VTach</td>
<td>Prospective observational cohort (retrospective control) VASO 40 units x 1 then EPI every 3-5 min vs. EPI every 3-5 min x 3 then VASO 40 units x 1 vs. EPI every 3-5 min</td>
<td>Results include both combo arms vs. only EPI: ↑ ROSC ↑ hospital admission ↑ 24 hr survival No difference in: Hospital discharge Neurologic outcomes</td>
</tr>
</tbody>
</table>

*All differences demonstrated statistical significance

OHCA: out-of-hospital cardiac arrest; VFib: ventricular fibrillation; DB: double blind; RCT: randomized controlled trial; EPI: epinephrine; VASO: vasopressin; ROSC: return of spontaneous circulation; hr: hour(s); IHCA: in-hospital cardiac arrest; MC: multi-centered; min: minute(s); CPR: cardiopulmonary arrest; ER: emergency room

F. Bottom line
i. Many studies included EPI administration in VASO arm
ii. Conflicting results on benefit of VASO over EPI
   a. Some reports of increasing ROSC and hospital admission
      1. Small studies
      2. Predominantly with repeat dosing of VASO
      3. Predominantly in asystolic patients

G. EPI + VASO vs. EPI
i. Stimulates both catecholamine and VASO receptors
   a. Improves perfusion of vital organs
   b. Decreases vasopressor-mediated adverse effects
ii. EPI + VASO diminishes cerebral microvascular blood flow
iii. Subgroup analysis suggests benefit in those requiring > 2 doses of initial vasopressor when VASO is combined with EPI
iv. Subgroup analysis suggests benefit of EPI + VASO in patients with pH < 7.2
Table 3. EPI + VASO vs. EPI

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<tbody>
<tr>
<td>Guyette et al. 2004</td>
<td>298</td>
<td>OHCA</td>
<td>Retrospective VASO administration determined by physician on scene EPI 1 mg every 3-5 min + VASO 40 units x 1 vs. EPI 1 mg every 3-5 min</td>
<td>↑ ROSC</td>
</tr>
<tr>
<td>Callaway et al. 2006</td>
<td>325</td>
<td>OHCA</td>
<td>Prospective, DB, RCT VASO 40 units x 1 vs. placebo x 1 after ≥ 1 EPI Followed by open label EPI</td>
<td>No difference in:</td>
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<td>ROSC</td>
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<td>Hospital arrival</td>
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<tr>
<td>Mally et al. 2006</td>
<td>598</td>
<td>OHCA</td>
<td>Prospective observational VASO 40 units then EPI 1 mg every 3 min vs. EPI 1 mg every 3 min</td>
<td>↑ petCO2; MAP</td>
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<td>Followed by open label EPI</td>
<td>↑ ROSC</td>
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<td>↑ 24 hr survival</td>
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<td>↑ neurologic outcome upon discharge</td>
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<td>(↑ hospital discharge in asystole subgroup)</td>
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<td>No difference:</td>
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<td>Hospital discharge</td>
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<tr>
<td>Gueguinaud et al. 2008</td>
<td>2894</td>
<td>OHCA resistant VFib/VTach</td>
<td>Prospective DB, MC, RCT VASO 40 units + EPI 1 mg every 3 minutes x 2 Followed by open label EPI</td>
<td>(↑ hospital discharge in PEA</td>
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<tr>
<td></td>
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<td></td>
<td>vs. EPI 1 mg + placebo every 3 minutes x 2 Followed by open label EPI</td>
<td>subgroup analysis)</td>
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<td>No difference in:</td>
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<td>ROSC</td>
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<td>Hospital admission</td>
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<td>Hospital discharge</td>
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<td></td>
<td>Neurologic recovery</td>
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<td></td>
<td>1 year survival</td>
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<tr>
<td>Cody et al. 2010</td>
<td>191</td>
<td>OHCA</td>
<td>Retrospective cohort evaluating protocols VASO 40 units + EPI 1 mg Followed by EPI 1 mg every 3-5min vs. EPI 1 mg every 3 min</td>
<td>No difference in:</td>
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<tr>
<td></td>
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<td></td>
<td>Followed by open label EPI</td>
<td>Hospital admission</td>
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<tr>
<td>Ducros et al. 2010</td>
<td>44</td>
<td>OHCA</td>
<td>Prospective, DB, RCT EPI 1 mg every 3 + VASO 40 units every 5 min vs. EPI 1 mg every 5 min vs. EPI 1 mg + VASO 40 units + nitroglycerin 300 mcg every 5 min</td>
<td>No difference in:</td>
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<td></td>
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<td></td>
<td>Followed by open label EPI</td>
<td>Diastolic BP</td>
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<tr>
<td>Ong et al. 2012</td>
<td>727</td>
<td>OHCA/IHCA (ED patients)</td>
<td>Prospective MC, DB, parallel, RCT VASO 40 units x 1 vs. EPI 1 mg x 1 Followed by open label EPI</td>
<td>↑ hospital admission (when variables accounted for)</td>
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<td>No difference in:</td>
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<td>Hospital discharge</td>
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</tbody>
</table>

*All differences demonstrated statistical significance

OHCA: out-of-hospital cardiac arrest; EPI: epinephrine; mg: milligram; min: minute(s); VASO: vasopressin; ROSC: return of spontaneous circulation; ER: emergency room; DB: double blind; RCT: randomized controlled trial; petCO2: end-tidal carbon dioxide; hr: hour; MC: multi-centered; mcg: micrograms; BP: blood pressure; IHCA: in-hospital cardiac arrest

I. Bottom line

i. Systematic reviews and meta-analyses failed to demonstrate benefit of VASO over EPI or in combination with EPI
   a. Secondary analysis suggests dose dependent increases in survival rates when treated with VASO vs. EPI in asystolic patients
   b. Largest OHCA study associated with mean time to medications > 20 minutes
ii. Meta-analysis 2014, reviewing 10 RCTs
   a. No improvement in ROSC, survival to hospital admission or discharge
b. IHCA subgroup analysis
   1. Higher ROSC
   2. Higher survival to hospital admission and discharge
   3. Favorable neurologic outcomes
   4. Non-traditional, repeated dosing of vasopressin
   5. All vasopressin, steroid, epinephrine (VSE) data

IV. Complications after ROSC

A. Adrenal insufficiency (AI) of CA\textsuperscript{11,44-52}
   i. Inability to adequately increase cortisol secretion in response to ACTH during and after ACLS
   ii. Etiology
      a. Adrenal gland ischemia
      b. Inflammatory response to ischemia results in further damage
   iii. Increases mortality
   iv. Diminishes response to catecholamines
   v. Leads to hemodynamic instability and circulatory collapse

B. Inflammatory mediated ischemic/reperfusion injury\textsuperscript{50,52-54}
   i. Activation of cytokines, endotoxins, and reactive species after CA
   ii. Inflammatory response further damages ischemic organs
      a. Compounds neurologic damage
      b. Cytokines associated with mortality and unfavorable neurologic outcomes
   iii. Normal physiologic response to cytokines is stimulation of cortisol release
      a. Unable to adequately respond due to AI

C. Post-resuscitation shock\textsuperscript{6,51,55-60}
   i. Precise definitions of hemodynamic instability/shock are lacking
   ii. Impaired contractile function and diastolic function that reverses several hours to days after resuscitation
   iii. Hyperdynamic phase, lasting minutes
      a. Tachycardia and hypertension
   iv. Post-resuscitation cardiovascular collapse phase
      a. Cardiac index (CI) and filling pressures are low
         1. Lactic acid produced
         2. Myocardial stunning results in left ventricular dysfunction
         3. Pro-inflammatory response resulting in loss of vascular tone
      b. Occurs several hours after CA
      c. Results in multi-system organ dysfunction which may progress to mortality
         1. Decreases cerebral blood flow
d. CI increases approximately 24 hours after arrest
   1. Independent of filling pressures or inotropic agents
e. Vasodilation continues and requires vasoactive drugs
   1. Recovery often seen within 3 days
v. Risk factors for development of post-resuscitation shock
   a. Fifteen minute time interval between onset of arrest and ROSC
   b. More frequent doses of EPI
   c. Greater number of defibrillation attempts
vi. Treatment
   a. Avoid hypotension
   b. AHA recommends maintaining systolic blood pressure $\geq 90$ mmHg and MAP $\geq 65$ mmHg
   c. Other authors advocate for more aggressive goals
      1. American Academy of Neurology and the Rocky Mountain Critical Care Conference recommend MAP goal of 80-100 mmHg
         aa. Based on expert opinion
         ab. Theoretical improvement in neurologic outcomes
d. Hemodynamic instability was not associated with worse neurologic outcomes when aggressively treated
   1. MAP goal $\geq 75$ mmHg
   2. Volume expansion based on left ventricle end diastolic pressure
   3. Vasoactive drugs: epinephrine or dobutamine with advanced hemodynamic monitoring

V. Steroids

A. Background\textsuperscript{8,13}
   i. Decrease inflammatory response and regulate homeostasis
   ii. No role for steroids in AHA or ERC guidelines
B. Cortisol plasma concentrations\textsuperscript{10,49,50,53}
   i. Normal range
      a. Without stress: 5-20 mcg/dL
      b. Under stress: 50-90 mcg/dL
   ii. Low levels during or after CA indicate lack of appropriate response
      a. Associated with early post-resuscitation mortality
   iii. Higher cortisol levels have been associated with neurologically intact survival and survival $> 1$ month
C. Mechanism of action\textsuperscript{11}
   i. Regulates gene expression
      a. Decreases production of kinins, histamines, liposomal enzymes, prostaglandins, leukotrienes
      b. Inhibits cell migration to area of injury
      c. Decreases vessel permeability
D. Physiologic effects\textsuperscript{11,13,20,41,42}
   i. Homeostasis
      a. Fluid and electrolyte balance
         1. Decreases cell apoptosis and provides positive inotropy through calcium homeostasis
      b. Maintains integrity of membrane structures
   ii. Anti-inflammatory
      a. Decreases ischemia/reperfusion injury
   iii. Vascular
      a. Decreases permeability, increases SVR
      b. Decreases production of vasodilators
      c. Increases vascular reactivity to catecholamines and angiotensin II
   iv. Cardiac
      a. Increases coronary perfusion pressure
         i. Increases production of coronary vasodilators
      b. Increases contractility
   v. Endocrine
      a. Supplements cortisol not produced during AI
E. Detrimental effects\textsuperscript{32}
   i. Electrolyte disturbances, sodium or glucose
   ii. Infections
   iii. Negative regulation on HPA axis, may result in AI
F. Dosing\textsuperscript{5,52,61}
   i. ACLS
      a. Hydrocortisone (HCT) 100 mg IV push once
      b. Methylprednisolone 40 mg IV push once
   ii. Stress dose steroids
      a. HCT 300 mg IV per day
G. Efficacy data

i. Animal data demonstrates increase ROSC with corticosteroids

Table 4. Steroids

<table>
<thead>
<tr>
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<th>Patients</th>
<th>Intervention</th>
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</tr>
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<tbody>
<tr>
<td>White et al. 1976</td>
<td>5</td>
<td>IHCA</td>
<td>Retrospective case series DEX 100 mg once after conventional therapy failed Plus: EPI, atropine, bicarbonate, isuprel Compared to historical control</td>
<td>Corrected rhythm **</td>
</tr>
<tr>
<td>White et al. 1979</td>
<td>25</td>
<td>IHCA</td>
<td>Retrospective case series DEX 100 mg once Plus: atropine, isoproterenol, EPI, calcium Compared to historical control</td>
<td>↑ ROSC **</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Refractory VFib or asystole</td>
<td></td>
<td>↑ long term survival **</td>
</tr>
<tr>
<td>Paris et al. 1984</td>
<td>86</td>
<td>OHCA</td>
<td>Prospective, RCT, DB Pre-hospital DEX 100 mg vs. placebo Plus: bicarbonate, EPI, and atropine</td>
<td>No difference in: ROSC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PEA</td>
<td>Retrospective Steroid use following ROSC for brain ischemia or lung injury Predominantly low dose DEX</td>
<td>Long term survival</td>
</tr>
<tr>
<td>Grafton et al. 1988</td>
<td>458</td>
<td>After OHCA VFib or asystole</td>
<td></td>
<td>No difference in: Regaining consciousness</td>
</tr>
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<td></td>
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<td></td>
<td>Hospital discharge</td>
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<tr>
<td>Tsai et al. 2006</td>
<td>97</td>
<td>OHCA</td>
<td>Prospective, non-randomized (required family member pre-approval) HCT 100 mg vs. placebo Plus: EPI, VASO in ~ 1/3</td>
<td>↑ ROSC</td>
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<td></td>
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<td>No difference in: Adverse effects Survival Neurologic function</td>
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</tbody>
</table>

*Unless specified, results demonstrated statistical significance  
** Statistical significance not evaluated

IHCA: in-hospital cardiac arrest; VFib: ventricular fibrillation; DEX: dexamethasone; EPI: epinephrine; CO: cardiac output; PEA: pulseless electrical activity; ROSC: return of spontaneous circulation; OHCA: out-of-hospital cardiac arrest; RCT: randomized controlled trial; HCT: hydrocortisone; VASO: vasopressin; min: minutes

H. Bottom line

i. Weakly associated with increases in ROSC  
a. Time dependent  
b. Driven by subgroup receiving hydrocortisone within 6 min of ED arrival or 22 min from collapse  
ii. No role for steroid administration following ROSC to treat brain ischemia  
iii. No increases in adverse effects

VI. VSE data

A. Is a cocktail of stress hormones the solution?

i. EPI has been the mainstay of ACLS drug therapy but is associated with consequences linked to worse outcomes after ROSC  
ii. VASO alone or in combination has not shown to be superior to EPI  
iii. VASO administration increases serum ACTH but does not result in an adequate physiologic response of cortisol  
iv. Evidence of relative AI and inflammatory mediated ischemia/reperfusion injury of CA linked to post-resuscitation shock which is known to increase mortality
B. Efficacy data


<table>
<thead>
<tr>
<th>Objective</th>
<th>Determine if VSE supplementation during and after resuscitation improves survival in refractory IHCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td><strong>Prospective</strong>, single-center, double blind, placebo-controlled, parallel group, randomized controlled trial</td>
</tr>
</tbody>
</table>
| Intervention: | • Methylprednisolone 40 mg x 1  
  • EPI 1 mg + VASO 20 units (per resuscitation cycle)  
  • Following ROSC, HCT 300 mg/day continuous infusion x 3-7 days, followed by taper, if post-resuscitation shock present |
| Control: | • Placebo x 1  
  • EPI 1 mg + placebo (per resuscitation cycle)  
  • Following ROSC, placebo x 3-7 days, followed by taper, if post-resuscitation shock present |
| Post-resuscitation shock: | - sustained > 4 hours, MAP ≤ 70 mmHg despite appropriate fluid resuscitation, or doubling of peri-arrest vasopressor requirements |
| Patients | Inclusion: IHCA with PEA/asystole or VFib/VTach after 2 defibrillation attempts  
Exclusion: pediatric, terminal illness, do not resuscitate order, arrest due to exsanguination, recent treatment with IV corticosteroids |
| Statistics | •ITT analysis  
  • Dichotomous variables: χ² or Fisher exact test  
  • Continuous variables: independent t test or Mann-Whitney exact test  
  • Linear mixed-model analysis for post-resuscitation shock  
  • Kaplan-Meier for survival  
  • Multivariate analysis for independent predictors of death |
| Results | VSE:  
  • n=100  
  • ↑ ROSC: 39/48 (81%) vs. 27/52 (52%) p=0.003  
  • ↑ survival to discharge: 9/48 (19%) vs. 2/52 (4%) p=0.02  
  • Following ROSC: ↑ MAP, ↓ vasopressor requirements, ↓ cytokine levels, ↑ central venous oxygen saturation, ↓ in lactate, ↑ renal-failure free days  
  Stress dose steroids:  
  • ↑ hospital discharge 8/27 (30%) vs. 0/15 (0%) p=0.02  
  • ↑ organ failure free days |
| Authors' Conclusions | VSE during resuscitation and stress-dose HCT in post-resuscitation shock improves survival by a factor of 4.5 in refractory IHCA |
| Critique | • Examined IHCA, did not exclude trauma patients  
  • Examined physiologic endpoints potentially associated with improvements in survival  
  • Predominantly asystole patients (75-80%)  
  • More reversible causes of CA in study group  
  • Use of multiple interventions; unclear if individual interventions are beneficial  
  • Used a previously unstudied dose of VASO  
  • Administered EPI and VASO every 2-3 minutes vs. 3-5 minutes  
  • Feasibility of administering VASO and EPI at the same time when not prepared ahead of time by study personnel |

C. Bottom line

i. Combination VSE demonstrates improvement in ROSC and survival to hospital discharge compared to EPI alone

ii. Benefits in ROSC likely from EPI + VASO

iii. Benefits in survival likely from methylprednisolone

iv. Neurologically favorable survival not demonstrated in this study
D. Efficacy data


<table>
<thead>
<tr>
<th>Objective</th>
<th>Determine if combination VSE improves outcomes compared to standard of care for IHCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Prospective, multi-centered, double blind, placebo-controlled, parallel-group, randomized controlled trial</td>
</tr>
</tbody>
</table>
| Intervention | Methylprednisolone 40 mg x 1  
| | EPI 1 mg + VASO 20 units (per resuscitation cycle)  
| | Following ROSC, HCT 300 mg/day continuous infusion x 3-7 days followed by taper, if post-resuscitation shock present |
| Control | Placebo x 1  
| | EPI 1 mg + placebo (per resuscitation cycle)  
| | Following ROSC, placebo x 3-7 days followed by taper, if post-resuscitation shock present |
| Patients | Inclusion: IHCA, requiring EPI  
| | Exclusion: pediatric, terminally ill, do not resuscitate orders, arrests due to exsanguination, current treatment with steroids |
| Statistics | ITT analysis  
| | Kolmogorov-Smirnov for normality  
| | Dichotomous variables: 2-sided χ², Fishers exact test  
| | Continuous variables: 2-sided t test, Mann-Whitney exact U test  
| | Bonferroni correction  
| | Linear mixed model analysis to determine effect of groups  
| | Logistical regression for ORs with 95% CIs  
| | Multivariable Cox regression for HRs with 95% CIs |
| Results | VSE:  
| | n=268  
| | ↑ ROSC: 109/130 (84%) vs. 91/138 (66%) p=0.005  
| | ↓ discharge with CPC score 1 or 2: 18/130 (14%) vs. 7/138 (5%) p=0.02  
| | ↓ duration ACLS, ↓ total EPI dose, ↑ hemodynamics, ↑ central venous oxygen saturation, ↑ cerebral perfusion pressure, ↑ renal, neurologic, ventilator-failure free days, ↓ organ dysfunction, similar adverse effects  
| | Stress dose steroids:  
| | ↑ discharge with CPC score of 1 or 2: 16/76 (21%) vs. 6/73 (8%) p=0.02  
| | 15 EPI patients received HCT, ↑ circulatory-, renal-, hepatic-, coagulation-, respiratory-failure free days  
| | No difference in incidence of adverse effects due to steroids |
| Authors’ Conclusions | VSE and stress-dose HCT vs. EPI results in ↑ survival to hospital discharge with favorable neurologic outcomes  
| | Post-arrest HCT may decrease poor outcomes, but requires further investigation |
| Critique | Examined IHCA, large sample, did not exclude all trauma patients  
| | CPR quality assessed with diastolic blood pressures  
| | Utilized CPC score to evaluate neurologically favorable survival  
| | Detailed protocol for treatment of underlying conditions, therapeutic hypothermia, sedation/analgesia, etc  
| | Predominantly asystolic medicine patients  
| | Chest compression cycles lasted approximately 3-4 minutes  
| | Frequent use of atropine and bicarbonate |

E. Bottom line

i. VSE increases ROSC and neurologically favorable survival  
   a. ROSC, number needed to treat (NNT)= 6  
   b. Neurologically favorable survival, NNT = 12

ii. Overall reduction in EPI doses, length of ACLS, improved peri-arrest hemodynamics and perfusion which results in improved long-term outcomes

iii. No increase in complications from steroids

iv. Medications administered approximately every 3-4 minutes
VII. Summary of evidence

A. Majority of studies are in OHCA vs. IHCA of non-traumatic origin and are powered for detecting differences in hospital admission

B. Many variables throughout studies over the years
   i. Time to initiation of BLS/ACLS
   ii. Variation in protocols of emergency responders
   iii. Unknown quality of chest compressions and approach to ventilatory support
   iv. Change in availability of AEDs and defibrillators
   v. Change in standard medications and doses

C. Many of the principles of therapy are based on data from previously healthy animals

D. Prior to VSE, no ACLS medication or combination of medications has improved survival to discharge or neurologically favorable survival

E. VSE demonstrated neurologically favorable survival

VIII. Conclusions

A. Addition of methylprednisolone complements EPI + VASO in improving ROSC rates
   i. Improves hemodynamic stability
   ii. Decreases ischemia/reperfusion injury
   iii. Reduces end-organ damage

B. Improves neurologic outcomes and overall survival in IHCA requiring vasopressors

IX. Recommendations

A. IHCA
   i. Administer methylprednisolone 40 mg IV x 1 during first compression cycle requiring medications
   ii. Alternate every compression cycle (2 minutes) between
      a. EPI 1 mg IV every 4 minutes
      b. VASO 20 units IV every 4 minutes
         1. Maximum of 5 doses
   iii. Continue standard use of other adjunctive treatments during ACLS when indicated based on clinical scenario

B. If ROSC is obtained, observe for post-resuscitation shock
   i. At minimum maintain a MAP of ≥ 65 mmHg consider goals of ≥ 75 mmHg
      a. After appropriate volume resuscitation
      b. After appropriate vasopressors are initiated
         i. If norepinephrine requirements ≥ 0.2-0.5 mcg/kg/min, consider additional stress dose steroids
         ii. Avoid inotropes


## Appendices

### Appendix A. “H’s & T’s” of Cardiac Arrest

<table>
<thead>
<tr>
<th>Cause</th>
<th>Indications</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypovolemia</td>
<td>Distributive shock</td>
<td>Crystalloids</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic shock</td>
<td>Crystals, EPI, H1RA, H2RA, steroids</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic shock</td>
<td>Blood products</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>↓ oxygen saturation, cyanosis, PEA</td>
<td>Oxygen</td>
</tr>
<tr>
<td>Hydrogen ion (acidosis)</td>
<td>↓ pH, ↓ CO2</td>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat underlying condition</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>↓ K ↓ Mg</td>
<td>K, Mg replacement</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>EKG progressing from peaked T waves to</td>
<td>Shift K:</td>
</tr>
<tr>
<td></td>
<td>absent P waves to prolonged PR and QRS</td>
<td>Calcium, insulin, dextrose</td>
</tr>
<tr>
<td></td>
<td>to sine-wave prior to loss of pulse</td>
<td>Sodium bicarbonate</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Core temp ≤ 30°C</td>
<td>Prevent additional heat loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rewarm</td>
</tr>
<tr>
<td>Tension pneumothorax</td>
<td>Tracheal deviation away from tension,</td>
<td>Needle decompression initially</td>
</tr>
<tr>
<td></td>
<td>tachycardia, tachypnea, hypoxia</td>
<td>Chest tube for definitive management</td>
</tr>
<tr>
<td></td>
<td>resulting in CA associated with</td>
<td>Pericardiocentesis – needle aspiration</td>
</tr>
<tr>
<td></td>
<td>PEA</td>
<td>Pericardial window – hole in pericardium</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>↓ ventricular filling and cardiac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>output causing hypotension and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ultimately CA</td>
<td></td>
</tr>
<tr>
<td>Toxins</td>
<td>Toxidrome presentations, patient</td>
<td>CCB/β blockers: calcium, glucagon, high dose</td>
</tr>
<tr>
<td></td>
<td>history, UDS or other laboratory</td>
<td>insulin/D50, fat emulsions</td>
</tr>
<tr>
<td></td>
<td>indicators</td>
<td>Digoxin: antidigoxin Fab antibodies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cyanide: hydroxocobalamin or sodium nitrite/sodium thiosulfate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local anesthetics: fat emulsion</td>
</tr>
<tr>
<td>Thrombosis (pulmonary)</td>
<td>Tachycardia, tachypnea prior to</td>
<td>Fibrinolitics and prolonged chest compressions</td>
</tr>
<tr>
<td></td>
<td>arrest, right heart strain, PEA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with rapid/narrow QRS, evidence of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td>Thrombosis (cardiac)</td>
<td>Chest pain, diaphoretic, EKG findings</td>
<td>Early coronary revascularization</td>
</tr>
<tr>
<td></td>
<td>prior to arrest, troponin elevation,</td>
<td>Fibrinolitics as a less favorable alternative</td>
</tr>
<tr>
<td></td>
<td>cardiac history</td>
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</tr>
</tbody>
</table>

### Appendix B. Guideline Concordant ACLS Medication Dosing

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>1 mg every 3-5</td>
<td>All rhythms</td>
</tr>
<tr>
<td></td>
<td>minutes</td>
<td>To replace the 1” or 2” dose of epinephrine per</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AHA guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All rhythms</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>40 units x 1</td>
<td>To replace the 1” or 2” dose of epinephrine per</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AHA guidelines</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1” dose: 300 mg x 1</td>
<td>Refractory VFib or VTach</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Per ERC guidelines: 900 mg IV drip over 24 hours</td>
</tr>
<tr>
<td></td>
<td>2” dose: 150 mg x 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 3-5 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 3-5 minutes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Per ERC guidelines:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>900 mg IV drip over</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 hours</td>
<td></td>
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</table>

All medications may be administered by IV or IO routes.
Appendix C. Cerebral-preformance Category

<table>
<thead>
<tr>
<th>CPC</th>
<th>Indicates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Conscious with normal function or only slight disability</td>
</tr>
<tr>
<td>2</td>
<td>Conscious with moderate disability</td>
</tr>
<tr>
<td>3</td>
<td>Conscious with severe disability</td>
</tr>
<tr>
<td>4</td>
<td>Comatose or in a vegetative state</td>
</tr>
<tr>
<td>5</td>
<td>Brain-dead or dead</td>
</tr>
</tbody>
</table>

References