Modern Management of Cardiac Arrest  
Guest: Dr. Joshua Reynolds

Background
- > 500,000 adults and children experience cardiac arrest (CA) annually in the US.
- CA claims more lives than colorectal cancer, breast cancer, prostate cancer, influenza, pneumonia, auto accidents, HIV, and firearms combined.
- Only 5% to 15% survive to hospital DC.

Hemodynamic-Directed Resuscitation
- ROSC and survival after CPR are dependent upon restoring myocardial blood flow.
- Coronary perfusion pressure (CPP) during relaxation phase of CPR is the primary determinant of myocardial blood flow.
- CPP = Aortic diastolic pressure – right atrial pressure
  1) Arterial line + central venous line
     a. Target CPP > 20 mm Hg
     b. Optimal CPP not established
  2) Arterial line only
     a. Target diastolic blood pressure > 25 mm Hg
     b. Improve quality of CPR or give vasopressors
  3) Capnography only
     a. Target ETCO2 > 20 mm Hg

- There are no human trials studying the optimal titration of these parameters
- Take Home Point: focus CA resuscitation on CPP

High-Quality CPR
- Background
  - The cornerstone of cardiac arrest resuscitation
  - Patient survival linked to quality of CPR
  - Goal is to deliver oxygen/substrate to vital tissues
  - Provides only 10-30% of normal coronary flow; 30-40% of normal cerebral flow
  - Providers frequently deliver compressions that are too slow, too shallow, and don’t allow for complete recoil
- Critical components
  - Chest compression fraction (CCF)
    ▪ CCF = proportion of time compressions are performed during arrest
    ▪ Target > 80%; lower CCFs assoc with decreased ROSC and survival to DC
    ▪ Minimize interruptions!
● Team Leader
  ○ Communicate clearly about impending pauses - direct team to perform simultaneous actions during pause

● Pulse checks
  ○ Manual palpation unreliable and results in long pause
  ○ Not recommended as a means of monitoring the effectiveness of CPR

● Airway
  ○ Optimal time for insertion of advanced airway unknown
  ○ Consider supraglottic airway or passive oxygenation
  ○ First attempt laryngoscopy during compressions; if unsuccessful, attempt to intubate in < 10 seconds

● Perishock pauses
  ○ Minimize preshock pauses
    ▪ Survival significantly lower for patients with preshock pause > 20 secs compared to preshock pause < 10 secs
    ▪ 18% reduction in survival for every 5 sec increase in preshock pause
  ○ Charge the defibrillator during compressions
  ○ Hands-on defibrillation?
  ○ Restart compressions immediately after shock and deliver for 1-2 min before postshock rhythm analysis

  ○ Rate
    ▪ AHA/ECC Guidelines recommend compression rate ≥ 100 /min
    ▪ Optimum target likely 100-120 /min
  ○ Depth
    ▪ Guidelines recommend compression depth ≥ 2 inches (50 mm) in adults; improved defibrillation success and ROSC
    ▪ Numerous studies demonstrating providers do not compress chest deep enough; depth < 38 mm associated with decreased ROSC/survival.
  ○ Chest Recoil
    ▪ Allow the chest to fully recoil
      ○ Animal data: improves MAP, CPP, myocardial blood flow
      ○ No studies in humans
    ▪ Avoid leaning: increases RA pressure, decreases cerebral and coronary perfusion, and decreases LV myocardial flow

● Mechanical CPR Devices
  ○ Theory: offers improved quality compressions while allowing defibrillation
    ▪ Meta-analysis
    ▪ Examines rates of ROSC from load-distributing band and piston-driven devices compared with manual CPR.
    ▪ 12 studies (6,538 patients; 1,824 with ROSC)
      ○ 8 load-distributing devices
- 4 piston-driven devices
  - Results
    - No benefit observed for piston-driven devices
    - 1 observational study demonstrated improved outcome for load-distributing device
        - Pragmatic, cluster-randomized, open-label trial of adults with non-traumatic OHCA in the UK.
        - Objective: determine if the introduction of the LUCAS-2 mechanical CPR into EMS response vehicles would improve survival over manual CPR.
  - Study
    - Patients
      - Adults > 18 years of age
      - Non-traumatic OHCA
    - Primary outcome: 30-day survival
  - Results
    - 4471 patients
      - 1652 assigned to LUCAS-2 device (638 did not receive)
      - 2819 assigned to the control group
    - 30-day survival
      - LUCAS-2 group: 6%
      - Control group: 7%
      - Take Home Point: no statistical difference in survival with mechanical devices.

Defibrillation
- Biphasic vs. monophasic devices: no difference in survival
- Deliver single shock then resume compressions before rhythm analysis

Airway & Ventilation
- Airway
  - Optimal timing of advanced airway placement is unknown
  - Prolonged attempts at airway management lead to interrupted compressions.
  - Consider delayed intubation, passive oxygen delivery via NRB mask during first few minutes of arrest.
  - Supraglottic airways: data is mixed regarding outcomes.
  - Use ETCO2 waveform capnography to confirm placement.
- Oxygenation
  - Administer 100% FiO2, though animal data indicates 100% FiO2 may result in worse outcomes compared with room air.
- Ventilations
  - Goal – provide sufficient oxygen without impeding perfusion during CPR
  - Positive-pressure ventilation lowers cardiac output and reduces CPP during CPR
  - Metabolic demands for oxygen are decreased in the arresting patient
  - Current recommendations: 8 – 10 bpm
  - Ventilate to produce no more than visible chest rise
End-tidal CO2

- CO2 levels can reflect tissue production, cardiac output, and ventilation
  - P – Position of the tube
    - Capnography superior to auscultation and capnometry
  - Q – Quality of CPR
    - Monitor for signs of fatigue in rescuer – drop in levels
  - R – ROSC
    - Sudden increase to normal (35-40 mm Hg) reliable indicator of ROSC
  - S – Strategy
    - Reduced levels described in patients with PE, tension PTX, and hemorrhage
  - T – Termination
    - ETCO2 < 10 mm Hg after 20 min predicts unsuccessful resuscitation.
    - Current data insufficient for specific cut-off values at certain time intervals.

Vasopressors

- Rationale: vasopressors increase aortic pressure w/o concomitant increase in RAP, thereby improving both coronary and cerebral perfusion pressure.
- Epinephrine reported to cause:
  - Decreased microcirculatory cerebral blood flow
  - Increased myocardial oxygen consumption
  - Increased post-defibrillation ventricular arrhythmias
  - Increased post-ROSC myocardial dysfunction
- Olasveengen TM, et al. JAMA 2009
  - Prospective, RCT of consecutive adults with OHCA in Oslo, Norway
  - Objective: determine whether removing IV drug administration from ACLS would improve survival to hospital DC after OHCA
  - Results
    - 851 patients (418 in ACLS group; 433 in no IV drugs group)
    - No statistical difference in survival to hospital DC or long-term survival
  - Double-blind, randomized, placebo-controlled trial of epinephrine in OHCA
  - Objective: determine the effect of epinephrine on patient survival to hospital DC
  - Results
    - 601 patients
    - ROSC 8.4% vs. 23.5% for those who got epinephrine
    - Survival to hospital DC 1.9% vs. 4% (not statistically significant)
  - Prospective, nonrandomized, observational propensity analysis of OHCAs occurring in Japan
  - Objective: evaluate the association between epinephrine use before hospital arrival and short- and long-term survival
  - Results
417,188 patients
- ROSC: 18.5% in the epinephrine group vs. 5.7% in no epi group
- Negative association between prehospital epi use and long-term mortality (adjusted OR 0.46)

  - Systematic review
  - 53 articles evaluating:
    - Any vasopressor to placebo
    - Vasopressin (w/ or w/o epinephrine) to epinephrine
    - High-dose epinephrine to standard dose epinephrine
    - Alternative vasopressors to epinephrine
  - Results
    - Epinephrine associated with improved rate of ROSC
    - No long-term benefit demonstrated
    - Alternative vasopressors (dopamine, phenylephrine, norepinephrine) provide no long-term survival benefit

  - Background
    - International guidelines recommend epinephrine every 3-5 minutes during cardiac arrest resuscitation.
    - However, epi may have adverse effects during post-resuscitation phase and contribute to myocardial dysfunction.
  - Objective: evaluate relationship between epinephrine and survival among cohort of patients with ROSC from out-of-hospital cardiac arrest.
  - Study
    - Observational cohort study
    - All patients with nontraumatic OHCA who achieved ROSC and were admitted to a large, single center in Paris.
    - Primary outcome: favorable neurologic outcome (CPC of 1 or 2) at discharge.
  - Results
    - 1556 patients
      - 1134 (73%) received epinephrine
        - Older
        - Less likely to have witnessed arrest
        - Less likely to present with shockable rhythm
        - Longer duration of resuscitation
      - 422 (27%) did not get epinephrine
        - PCI performed in 44%, hypothermia performed in 70%
    - Survival
      - Epinephrine group: 193/1134 (17%)
      - No epinephrine group: 255/422 (60%)
      - Epinephrine use was negatively associated with favorable neurologic survival (adjusted OR 0.32).
      - Adverse association of epinephrine persisted across subgroups defined by initial rhythm, length of resuscitation, and post-arrest care.
Patients who received epinephrine within first 9 min of arrest had a better outcome (aOR 0.54) than those who received between 10-15 min (aOR 0.33).

Limitations: observational design, single center

Combinations

- Mentzelopoulos SD, et al. JAMA 2013
  - Randomized, double-blind, placebo-controlled, parallel-group trial
  - Objective: to determine whether the combination of vasopressin-epinephrine-corticosteroids during and after CPR improved survival to hospital DC in IHCA patients.
  - Results
    - 268 patients (VSE group: 130; control group: 138)
    - VSE group had higher probability for ROSC and survival to hospital DC with good neurologic outcome (13.9% vs. 5.1%)

Take Home Points

- No definitive evidence that any vasoactive drugs improve long-term survival.
- No definitive evidence that any antiarrhythmic (i.e., amiodarone) has improved survival to hospital DC.

Unproved Therapies

- Calcium
  - Theory: acidosis during cardiac arrest may cause hypocalcemia that, if corrected, it may restore cardiac function during arrest.
    - Systematic review
    - 10 articles (2 RCTs); most studies rated as ‘fair’ quality
    - No evidence that calcium in cardiac arrest resuscitation improves survival regardless of presenting rhythm
  - Consider in cases of hyperkalemia, hypocalcemia, calcium channel blocker overdose, hypermagnesemia

- Thrombolytics
  - Theory: large % of patients with OHCA are due to ACS or PE
    - Double-blind, multicenter trial in adults with OHCA
    - Randomized to tenecteplase or placebo
    - Primary outcome: 30-day survival
    - Results
      - 1050 patients (525 to tenecteplase)
      - 30-day survival
        - Tenecteplase group: 14.7%
        - Placebo group: 17%
    - Trial terminated early for no benefit

- Active Compression-Decompression CPR
  - Active compression-decompression CPR uses a device with a suction cup to perform CPR; differs from traditional CPR where chest is allowed to passively recoil.
  - Initial small studies demonstrated possible improvement in mortality and neurologic injury.
- Systematic review
- 10 trials (8 OHCA, 1 INHCA, 1 both)
- OHCA – 4162 patients
- No difference in mortality or neurologic impairment between ACDR CPR and standard CPR.

Aminophylline
- Bradyasystole is most common initial rhythm in OHCA.
- Survival from ‘nonshockable’ rhythms is very poor (< 3%).
- Theory: aminophylline believed to counteract the effects of endogenous adenosine and may lead to improved survival.
  - Systematic review of all RCTs comparing IV aminophylline with administered placebo in adults with non-traumatic, normothermic, bradyasystolic cardiac arrests.
  - 5 trials (1254 patients; risk of bias low in 4 studies)
  - Aminophylline had no effect on survival to hospital admission, ROSC, or survival to DC.

Refractory Cardiac Arrest - Novel Therapies

Definition
  - Retrospective cohort study of cardiac arrest database (ROC) at single center (Pittsburgh site)
  - Objective: to determine the duration of CPR after which repeated traditional interventions cease to result in meaningful survival.
  - Study
    - Patients
      - Adults > 18 years of age with non-traumatic OHCA
      - Received chest compressions from professional provider or rescue shocks
    - Primary endpoint: survival to hospital DC with favorable neurologic status (mRS 0-3)
  - Results
    - 1014 patients
    - 47% achieved ROSC, 11% survived to hospital DC, 6% had a favorable functional status
    - 90% of patients who had favorable neurologic status at hospital DC had ROSC within 16 minutes
  - Limitations: single center, retrospective cohort of database
  - Take Home Points
    - Conventional resus strategies most effective w/in 10-15 min.
    - After 15 min, prob. of good functional recovery falls to < 2%.

ECLS
- Background
  - Literature on ECLS for refractory cardiac arrest present since 1980s
  - Most of literature for OHCA limited to small case series/case reports often comparing to historical controls.
- **Kagawa, et al. Circulation 2012**: 42 pts, 21% survival with good neurologic outcome
- **Maekawa, et al. Crit Care Med 2013**: 53 pts; 32% survival
- **Leick, et al. Clin Res Cardiol 2013**: 28 pts; 39% survival
- Large randomized controlled trials have not yet been completed
- Extracorporeal Life Support Organization Registry
  - Over 5600 patients received ECLS for cardiac arrest
  - 1657 received ECPR: 28% survival to hospital DC
- Growing body of literature on use of ECLS in ED
  - **Bellezzo JM, Shinar Z, et al. Resuscitation 2012**: 18 patients, 8 survived to hospital DC, 5 neurologically intact

### Recent Literature

  - Objective: How does ECPR effect neurologic outcomes for patients with OHCA
  - Study: prospective observational study of 46 facilities in Japan (26 assigned to ECPR, 20 assigned to CPR)
  - Inclusion
    - Adults 20 – 75 years of age
    - VF/VT on initial ECG
    - CA on hospital arrival w/ or w/o pre-hospital ROSC
    - Arrival to ED within 45 min from 911 call
    - No ROSC at least during the 15 min after hospital arrival
  - Outcome: Favorable neurologic status (CPC 1 or 2) at 1 month and 6 months after CA
  - Results - 454 patients (234 in ECPR; 159 in CPR)
    - 1 m favorable outcomes (12.3% ECPR vs. 1.5% in CPR)
    - 6 m favorable outcomes (11.2% in ECPR vs. 2.6% in CPR)
    - Limitations
      - Differences in care between facilities
        - TH: 91.5% in ECPR vs. 54%
        - IABP: 92.7% in ECPR vs. 62.2%
        - Coronary angio: 89% in ECPR vs. 68%
    - Non-randomized study
- **Stub D, et al. The CHEER trial. Resuscitation 2014**
  - Study: prospective, pilot study from single center in Melbourne, Australia (The Alfred Hospital)
  - Patients (OHCA + IHCA)
    - OCHA
      - Aged 18-65 years
      - Cardiac arrest due to suspected cardiac etiology
      - CPR w/in 10 min by bystanders or EMS
      - Initial rhythm of VF
      - Mechanical CPR machine
  - Protocol
Eligible after 30 min of persistent cardiac arrest
- 2L iced saline infused with mechanical CPR device
- Intubated with 100% FiO2
- Epinephrine 1 mg every 4 min
- ECMO
  - 2 CCM physicians
  - Cannulated femoral artery and vein
  - Heparin bolus, blood flow at 3L/min with oxygen gas flow 3L/min
  - MAP of 70 mm Hg targeted with epi infusion
- Transported to the cardiac catheterization lab

● Results
  - 26 patients (11 OHCA and 15 IHCA)
    - Initial rhythm VF in 11 OCHA
    - Underlying cause of arrest ACS in 73%
  - Median time from collapse to ECMO initiation: 56 min
  - ROSC: 92%
  - Survival to hospital DC: 56%
    - 5/11 (45%) for OHCA
    - All survivors DC with full neurologic recovery

● Complications
  - Blood transfusion required in 69%
  - Vascular surgery required in 42% - fem artery repair; arterial backflow cannula placement, ischemic limb

- Study: analysis of single center prospective registry (U Penn)
- Objective: describe the institution’s experience with ECLS as a rescue strategy in adults with OHCA.

● Patients
  - Age 18-70
  - Witnessed arrest (out-of-hospital, in the ED, or shortly after arrival to inpatient unit or cardiac cath lab)
  - Bystander initiated CPR
  - VF or VT as initial rhythm or obvious cardiac cause
  - Collapse to EMS arrival < 15 min

● Results
  - 26 patients (15 OHCA, 5 in the ED, 3 after arriving to inpatient unit, 3 en route for transfer)
  - 42% with VF or pulseless VT
  - Average time from arrest to initiation of ECLS: 77 min
  - All patients cannulated via the femoral artery, femoral vein, or internal jugular vein
  - 4 patients (15%) survived to DC; 3 neurologically intact
  - 69% suffered complications: ischemia to lower extremity, stroke, hemorrhage, and organ failure.

● Limitations
  - Retrospective, observational case series
  - Protocol developed largely by consensus
- Low rate of VF/pulseless VT as initial rhythm
- Low rates of bystander CPR

- ECLS Take Home Points
  - No RCT or universally accepted protocol
  - Resource intensive therapy
  - Best outcomes appear to be adults with witnessed arrest, bystander CPR w/in minutes, shockable rhythm, short EMS transport time, short time to initiation of ECMO, rapid cooling once ECMO initiated, and emergent cardiac catheterization.
  - High rate of complications: hemorrhage, ischemia to lower extremity, and arterial injuries.

- Esmolol
    - Patients in cardiac arrest have high levels of endogenous and exogenous epinephrine.
    - The $\beta_1$ and $\beta_2$ effects of epinephrine can increase myocardial oxygen requirements, worsen ischemic injury, lower VF threshold, worsen post-ROSC myocardial function
    - Objective: compare outcomes of patients who received esmolol to those who did not during refractory VF arrest in the ED.
    - Study
      - Retrospective, observational, analysis
      - Single, urban, academic county hospital (Hennepin County Medical Center)
    - Patients
      - Initial rhythm of VF or pulseless VT
      - CA in the ED or prehospital setting and remained in CA in ED
      - Received at least 3 defibrillation attempts
      - Got 300 mg amiodarone and 3 mg epinephrine
      - Had manual CPR by EMS followed by automated CPR with LUCAS device
      - All intubated
    - Results
      - 25 patients (6 received esmolol)
      - Esmolol group
        - All achieved temporary ROSC
        - 4 of 6 achieved sustained ROSC; all taken to Cath Lab
        - 3 of 6 survived to DC with good neurologic outcomes
      - No esmolol group
        - 8 of 19 achieved temporary ROSC
        - 6 survived to ICU admission
        - 2 survived to DC with good neurologic outcomes
    - Limitations: retrospective, small sample size

References:
12. Reynolds JC. Modern management of cardiac arrest.