Cruising the 2021 Critical Care Literature...A Year in Review

Cardiac Arrest


- **Objective**
  - Report on long-term survival, quality of life, and neurocognitive outcome in survivors of OHCA enrolled in the PARAMEDIC2 Trial
    - PARAMEDIC2 Trial
      - Randomized, double-blind, controlled trial
      - 5 EMS agencies in the UK
      - OHCA patients where ACLS was initiated
      - Randomized to epinephrine or placebo
      - Primary Outcome: 30-day survival

- **Study**
  - Evaluated both 6- and 12-month survival using various validated surveys (mRS, MMSE, TSQ, and IQCODE-CA)

- **Results**
  - 6-month survival
    - Epinephrine Group: 2.9%
    - Placebo Group: 2.1%
  - 6-month survival with favorable neurologic outcome
    - Epinephrine Group: 2.0%
    - Placebo Group: 1.5%
    - Severe neurologic impairment more common in those who got epinephrine (22.8% vs. 13.4%)
  - 12-month survival
    - Epinephrine Group: 2.7%
    - Placebo Group: 2.0%
    - No difference in favorable neurologic survival

- **Take Home Point**
  - Epinephrine improved both 6- and 12-month survival but did not demonstrate improvement in favorable neurologic outcome


- **Objective**
  - Does the administration of calcium during OHCA improve ROSC.

- **Study**
  - Randomized, placebo-controlled, parallel group, double-blind, superiority trial
  - Took place in Denmark
  - Patients – Included
- Adults 18 years of age or greater
- OHCA
- Received at least 1 dose of epinephrine

**Intervention – Randomized 1:1**
- **Calcium Group**
  - 5 mmol of calcium chloride
  - IV or IO
  - Immediately after first dose of epinephrine
  - Second dose could be given after 2nd epinephrine dose
- **Placebo Group**
  - 9 mg/mL of sodium chloride

**Primary Outcome**
- Sustained ROSC for at least 20 minutes

**Secondary Outcomes**
- Survival at 30 days
- Survival at 30 days with favorable neurologic outcome

**Results**
- Trial stopped early after 383 patients enrolled (planned for 674 patients)
  - Calcium Group: 193 patients
  - Placebo Group: 198 patients
- Patient characteristics well balanced
  - 29% female
  - 82% had OHCA
  - 75% had a shockable rhythm
  - Median time from OHCA to study drug: 18 min
- **Primary Outcome – Sustained ROSC**
  - Calcium Group: 19%
  - Placebo Group: 27%
  - Not statistically different
- **Secondary Outcome – Survival at 30-days**
  - Calcium Group: 5.2%
  - Placebo Group: 9.1%
  - Not statistically different
- **Secondary Outcome – Survival at 30-days with favorable neurologic outcome**
  - Calcium Group: 3.6%
  - Placebo Group: 7.6%
  - Not statistically different

**Limitations**
- Trial stopped early
- OHCA
- Excluded tox cases (calcium channel blocker OD) and hyperkalemia

**Take Home Point**
- Administration of calcium did not improve sustained ROSC rates in OHCA patients

To determine whether the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest improve return of spontaneous circulation.

- **Study**
  - Randomized, placebo-controlled, parallel group, double-blind, superiority trial
  - 10 hospitals in Denmark
  - Patients - Included
    - 18 years of age or older
    - IHCA
    - Received at least 1 dose of epinephrine during cardiac arrest
  - Patients randomized in a 1:1 ratio
    - Vasopressin / Methylprednisolone Group
      - 20 IU vasopressin
      - 40 mg of methylprednisolone
      - Given as soon as possible after the first dose of epinephrine
      - Additional doses could be administered after each epi dose for a max of 4 doses
    - Placebo Group
      - Ampules of sodium chloride
  - Primary Outcome
    - Return of spontaneous circulation for at least 20 minutes
  - Secondary Outcomes
    - Survival at 30 days
    - Favorable neurologic outcome at 30 days

- **Results**
  - A total of 501 patients were included in the analysis
    - Vasopressin / Methylprednisolone Group: 237 patients
    - Placebo Group: 264 patients
    - Baseline characteristics were similar between the groups
  - Primary Outcome - ROSC
    - Vasopressin / Methylprednisolone Group: 42%
    - Placebo Group: 33%
    - Risk Ratio of 1.30 (95% CI 1.03-1.63; p=0.03)
    - Fragility Index = 3
  - Secondary Outcomes
    - 30-day Survival
      - Vasopressin / Methylprednisolone Group: 9.7%
      - Placebo Group: 12%
      - Not statistically significant
    - Favorable neurologic outcome
      - Vasopressin / Methylprednisolone Group: 7.6%
      - Placebo Group: 7.6%
      - Not statistically significant
    - Favorable neurologic outcome at 30 days
      - Vasopressin / Methylprednisolone Group: 4.6%
      - Placebo Group: 7.2%
      - Not statistically significant

- **Limitations**
  - Large number of patients screened, but only 501 patients ultimately included
  - Though multicenter, took place only in Denmark
  - Primary outcome was ROSC, not favorable neurologic survival at discharge
Some differences occurred between patients in the post-resuscitation period.
90% of patients had an initial nonshockable rhythm

Take Home Points
- Among IHCA patients, the administration of vasopressin and methylprednisolone resulted in a significant increase in ROSC, however did NOT improve survival at 30 days and survival with favorable neurologic outcome.
- The use of vasopressin and steroid for patients with IHCA, and OHCA, requires further study and is not ready for standard care.

Post-Arrest Care

Objective
- To determine whether OHCA patients with ROSC but without ST-segment elevation benefit from immediate coronary angiography for treating or ruling out acute coronary events.

Study
- Investigator-initiated, randomized, multicenter, open-label trial
- Conducted in 31 centers in Germany and Denmark
- Patients - Included
  - At least 30 years of age
  - Resuscitated from OHCA of possible cardiac origin
  - Shockable or nonshockable rhythm
  - No ST-segment elevation on ECG
- Interventions
  - Immediate Coronary Angiography
    - Transferred to the cath lab as soon as possible after hospital admission
  - Delayed Coronary Angiography
    - First transferred to the ICU for further treatment and evaluation of the etiology of OHCA
    - Could proceed to cath after a minimum delay of 24 hours depending on the results of further testing and treatment
    - Cath within 24 hours in this group was permitted for:
      - Substantial increase in troponin
      - Electrical instability
      - Cardiogenic shock
      - New ST-segment elevation
- Primary Outcome
  - 30-day all-cause mortality
- Secondary Outcomes
  - MI at 30 days
  - Severe neurologic deficit (CPC 3 to 5) at 30 days
  - ICU LOS
  - Rehospitalization within 30 days for CHF
  - Moderate or severe bleeding
  - Stroke
  - AKI leading to RRT

Results
- Total of 558 patients eligible for randomization; 554 ultimately included in the trial
  - Immediate Coronary Angiography: 281 patients
Delayed Coronary Angiography: 273 patients
Patient characteristics well balanced

Interventions
- Immediate Coronary Angiography
  - Performed in 96% of patients
  - Median time from arrest to cath: 2.9 hrs
  - Prevalence of CAD was 61%
  - Revascularization occurred in 40%
- Delayed Coronary Angiography
  - Performed in 62% of patients
  - Median time from arrest to cath: 46.9 hours
  - Prevalence of CAD was 72%
  - One or more coronary lesions considered responsible in 40%
  - Revascularization occurred in 43%

Primary Outcome (30-day all-cause mortality)
- Immediate Coronary Angiography: 54%
- Delayed Coronary Angiography: 46%
- p=0.06

Secondary Outcomes
- No difference in MI at 30-days, severe neurologic deficit at 30-days, ICU LOS, rehospitalization for CHF at 30-days, need for RRT, CVA, or bleeding.
- A composite outcome of all-cause mortality or severe neurologic deficit favored delayed coronary angiography

Limitations
- Open-label: physicians/ICU staff were aware of treatment allocation which may have influenced further treatment
- Excluded in-hospital cardiac arrest and those with ST-segment elevation, electrical, or hemodynamic instability
- 22 patients randomized to delayed coronary angiography got a cath under 24 hours despite no protocol indication

Take Home Points
- Among OHCA patients with ROSC and no evidence of ST-segment elevation on ECG there was no benefit to immediate coronary angiography compared with delayed angiography after ICU admission.


Objective
- To assess the beneficial and harmful effects of hypothermia as compared with normothermia and early treatment of fever in patients after cardiac arrest.

Study
- International, investigator-initiated, superiority trial
- Performed in 61 centers in 14 countries
- Patients - Included
  - Adults ≥ 18 years of age
  - Admitted to the hospital after OHCA of a presumed cardiac or unknown cause
  - Any initial rhythm
  - More than 20 consecutive minutes of ROSC
  - Remained unconscious and unable to follow verbal commands
- Hypothermia
Immediately cooled to 33 C (cold IVFs, surface device, or intravascular device)
- Maintained for 28 hours
- Rewarmed to 37 C in hourly increments

- **Normothermia**
  - Maintain temperature of 37.5 C or less
  - If temperature reached > 37.8 C, cooling with surface or intravascular devices was initiated to target a temperature of 37.5 C
  - No active warming or cooling was initiated for patients who had a spontaneous temperature < 37.8 C

- **Neuroprognostication**
  - Performed at 96 hours after randomization or later

- **Primary Outcome**
  - All-cause mortality at 6 months

- **Secondary Outcomes**
  - Poor functional outcome at 6 months (mRS of 4 to 6)
  - Number of days alive and out of the hospital until 180 days
  - Health-related quality of life

- **Adverse Events**
  - Pneumonia
  - Sepsis
  - Bleeding
  - Arrhythmia resulting in hemodynamic compromise

### Results
- 1861 patients included in the intention-to-treat population
  - Hypothermia Group: 930 patients
  - Normothermia Group: 931 patients

- **Primary Outcome** – All-cause mortality at 6 months
  - Hypothermia Group: 50%
  - Normothermia Group: 48%
  - RR with hypothermia 1.04 (95% CI 0.94 to 1.14; p=0.37)
  - Consistent across subgroups (gender, age, initial rhythm, shock present on admission)

- **Secondary Outcome** – Poor functional outcome at 6 months
  - Hypothermia Group: 55%
  - Normothermia Group: 55%
  - RR with hypothermia 1.00 (95% CI 0.92 to 1.09)

- **Adverse Events**
  - Arrhythmias
  - Hypothermia Group: 24%
  - Normothermia Group: 17%
  - No difference in pneumonia, sepsis, or bleeding were observed

### Limitations
- Elements of ICU care (sedation, paralysis, mechanical ventilation) included in the trial protocol many not be representative of common clinical practice
- Non-blinded
- No control group without TTM was included (almost 50% in the Normothermia Group had TTM applied to keep temp below target)

### Take Home Point
- TTM to target a temperature of 33 C did not lower 6-month all-cause mortality in patients with OHCA compared to those treated with TTM to target normothermia.

- **Objective**
  - To compare the effect of using a bougie vs an endotracheal tube with stylet on outcomes of tracheal intubation in EDs and ICUs across multiple health systems.

- **Study**
  - Randomized, pragmatic, parallel-group, unblinded trial
  - 15 sites: 7 EDs and 8 ICUs in 11 US hospital
  - Patients - Included
    - Undergoing tracheal intubation
    - Planned use of sedation and a nonhyperangulated blade
  - Intervention
    - Bougie Group
      - Operators instructed to use a bougie for the first attempt at intubation
    - Stylet Group
      - Use an ETT with a malleable stylet for first attempt at intubation
      - Shape stylet with a distal bend of 25-35 degrees
  - Primary Outcome
    - Successful intubation on the first attempt
  - Secondary Outcomes
    - Incidence of severe hypoxemia between induction and 2 min after intubation
    - Defined as SpO2 < 80%

- **Results**
  - 1102 patients for the primary analysis
    - Bougie Group: 556 patients
    - Stylet Group: 546 patients
  - Baseline characteristics were similar between the groups
    - Most common reasons for intubation: altered mental status and acute respiratory failure
    - Most common operator was EM (63%)
    - Most operators were resident physicians (62%)
    - Operators had performed a median of 60 total intubations
  - Primary Outcome – First pass success
    - Bougie Group: 80.4%
    - Stylet Group: 83%
    - No significant difference
    - No significant difference in the adjusted analysis or between any prespecified subgroups
  - Secondary Outcome – Severe hypoxemia
    - Bougie Group: 11%
    - Stylet Group: 8.8%
  - Airway complications – post-intubation pneumothorax
    - Bougie Group: 2.5%
    - Stylet Group: 2.7%
  - Cardiovascular collapse
    - Bougie Group: 12.2%
    - Stylet Group: 16.7%
Limitations
- Excluded patients for whom urgency of intubation precluded randomization
- Excluded use of hyperangulated laryngoscope
- Excluded patients for whom use of a bougie was indicated
- Most operators in the trial had limited experience using a bougie
- Unblinded trial
- Did not evaluate the use of bougie as a rescue device after failed first attempt

Take Home Points
- Among critically ill adults undergoing tracheal intubation, use of a bougie did not significantly increase the incidence of successful intubation on the first attempt compared with ETT with stylet.

Post-Intubation Sedation

Objective
- Estimate the prevalence of awareness with paralysis in ED patients receiving mechanical ventilation

Study
- Prospective, cohort study
- Single-center, academic, residency-affiliated, tertiary care center in St. Louis, MO
- Patients - included
  - Adults aged 18 years or older
  - Underwent mechanical ventilation through an ETT in the ED
  - Intubation could have been performed either in the ED, prehospital setting, or at a transferring facility
- Methods of Measurement
  - All measurements and clinical data were gathered from chart review – all variables extracted from the EMR
- Primary Outcome
  - Awareness with paralysis
  - Investigators used a combination of questions from the Brice questionnaire, and the ICU Memory Tool.
  - Brice questionnaire is the preferred method for evaluating awareness with paralysis
- Secondary Outcome
  - Perceived threat (identified as a mediator or causal pathway to PTSD symptoms)
  - Assessed using a validated measurement tool

Results
- 383 patients included in the study
- 27 patients reported memories of wakeful paralysis and were evaluated for the primary outcome
- After adjudication, the prevalence of possible or definite awareness with paralysis was 2.6% (95% CI 1.3% to 4.7%)
- Exposure to rocuronium at any time in the ED (RSI and postintubation) was significantly different between patients who experienced awareness with paralysis (70%) versus the rest of the cohort (31%) (OR 5.1; 95% CI 1.3 to 20.1)

Limitations
- Overall sample size was small
Single-center
Subjective assessment of awareness with paralysis
Authors excluded a large number of neurologically injured patients
Assessed patients before hospital DC – did not assess them later (i.e., 30 days)

- **Take Home Points**
  - WATCH OUT for prolonged paralysis and no sedation!
  - Awareness with paralysis occurred in 2.6% of this single center cohort of ED patients receiving mechanical ventilation and was associated with rocuronium exposure.
  - Given the volume of patients intubated in the ED annually in the US, this could suggest that thousands of patients may have awareness with paralysis.

**Cardiogenic Shock**

- **Objective**
  - To compare the efficacy and safety of milrinone and dobutamine in patients with cardiogenic shock in a pragmatic randomized clinical trial.

- **Study**
  - Randomized, double-blind clinical trial
  - Single quaternary cardiac care unit at the University of Ottawa
  - Patients – Included
    - 18 years of age or older
    - Admitted to the cardiac ICU
    - Had cardiogenic shock, as defined by the Society for Cardiovascular Angiography and Interventions definition
  - Trial Procedures
    - Assigned in a 1:1 fashion to receive either milrinone or dobutamine
    - Once randomized, patients received the medication in a concealed bag at a dose from “stage 1 to stage 5”.
      - For milrinone, this corresponded to a dose range of 0.125, 0.250, 0.375, 0.500 and > 0.500 mcg/kg/min
      - For dobutamine, this corresponded to a dose range of 2.5, 50., 7.5, 10.0, and > 10.0 mcg/kg/min
  - Primary Outcome - composite outcome of:
    - In-hospital death from any cause
    - Resuscitated cardiac arrest
    - Receipt of cardiac transplant or mechanical circulatory support
    - Nonfatal MI
    - TIA or CVA
    - Initiation of RRT
  - Secondary Outcomes
    - LOS in the cardiac ICU
    - Arrhythmia requiring intervention
    - Total duration of inotropic duration
    - Total hospital LOS

- **Results**
  - Total of 192 were ultimately enrolled
  - Primary Outcome
    - Dobutamine group: 54%
    - Milrinone group: 49%
- RR 0.90
- 95% CI 0.69 to 1.19; p=0.47
- No effect on prespecified subgroups including affected ventricle or concomitant use of vasopressors
  - Secondary Outcomes
    - No difference in the individual components of the composite primary outcome
    - No difference in total duration of inotropic support, hospital and ICU LOS
    - No difference in arrhythmias that required intervention
    - No differences in heart rate, MAP, serum lactate/creatinine, or urine output

- Limitations
  - Single center study – limiting generalizability
  - Dose adjustments based on physician judgment and not a standard study protocol
  - Only in-hospital outcomes were evaluated
  - Time from ICU admission to randomization up to 24 hours in some patients (is this too long?)
  - Power calculations based on a fairly large difference between milrinone and dobutamine (20% difference)

- Take Home Points
  - The DOREMI trial did not find a significant difference between milrinone and dobutamine for patients with cardiogenic shock.

Fluid Resuscitation

- Objective
  - To assess whether the administration of a balanced solution (Plasma-Lyte 148) during the ICU stay compared with NS would improve 90-day mortality in critically ill patients.

- Study
  - Investigator-initiated, randomized clinical trial
  - Conducted in 75 ICUs in Brazil
    - Patients - Included
      - Admitted to an ICU
      - Needed at least 1 fluid expansion at the discretion of the attending physician
      - Were not expected to be discharged the next day
      - Met at least 1 of the following:
        - Older than 65 years of age
        - Had hypotension (MAP < 65 mm Hg or SBP <90 mm Hg) or pressors
        - Sepsis
        - Required NIV or MV for at least 12 hours
        - Early signs of kidney dysfunction
        - Cirrhosis or acute liver failure
  - Randomization – patients randomized to receive either 0.9% NS or balanced solution
  - Interventions
    - Fluids supplied in identical 500 ml bags
    - Physicians, patients, and those who assessed outcomes blinded to assigned treatment
    - Overall patient management left to the discretion of the attending physician
Primary Outcome
- 90-day survival

Secondary Outcomes
- Need for RRT up to 90-days after enrollment
- Occurrence of AKI
- SOFA score assessed at a continuous value and individual components at days 3 and 7
- Number of days not requiring MV within 28 days

- Results
  - Ultimately, 10,520 patients included in the analysis (5,230 randomized to balanced solutions; 5,290 randomized to saline solution)
  - Interventions
    - Patients in both groups received a median of 1.5 L of fluid during the first day of enrollment
    - Accumulated median fluid during the first 3 days was 4.1 L
  - Primary Outcome: 90-day mortality
    - Balanced solution group: 26.4%
    - 0.9% NS group: 27.2%
    - HR 0.97 (95% CI 0.90 to 1.05) p=0.47
  - Secondary Outcomes
    - Only 2 were found to be statistically significant
    - SOFA Score at 7 days different for the balanced solution group (median difference 0.27) mostly due to a higher neurologic SOFA score

- Limitations
  - High number of elective surgical admissions to the ICU
  - Overall lower mortality for study patients than initially planned/designed. Patients had lower illness severity scores
  - Patients received a relatively small amount of IVFs
    - 1.2 L on the first ICU day
    - 2.9 L during the first 3 days
  - Almost 70% received IVFs before enrollment, of which 45% had > 1 L
  - Only evaluated Plasma-Lyte 148

- Take Home Points
  - “Among critically ill patients requiring fluid challenges, the use of a Plasma-Lyte 148 compared with 0.9% NS did not significantly reduce 90-day mortality.”