Ameliorating Reperfusion Injury During Resuscitation from Cardiac Arrest

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Objectives

- Discuss the role of reperfusion injury in resuscitation from cardiac arrest
- Describe ischemic conditioning as a way to ameliorate reperfusion injury
- Review mechanical and pharmacologic approaches to ischemic postconditioning
Background

- Ischemic time (downtime) one of the most important predictors of outcome in sudden cardiac arrest (SCA)
- Reperfusion injury occurs to vulnerable cells after the abrupt restoration of blood flow to previously ischemic tissue
- Accounts for approximately 50% of total cell damage in animal models
3-Phase Time-Sensitive Model

- Electrical Phase
  - 4 min

- Circulatory Phase
  - 10 min

- Metabolic Phase...

Reperfusion Injury

Weisfeldt ML, Becker LB, JAMA 2002, 288(23):3035-3038
Clinical Manifestations of Non-Lethal IR Injury

- Myocardial stunning
- Reperfusion arrhythmias
- Worsened sensory, motor cognitive function
- Multiorgan Dysfunction Syndrome
Contributors to IR injury

- pH
- Intracellular Ca\(^{2+}\) overloading
- Intracellular oedema
- Oxidative stress
- Mitochondrial permeability transition pore opening
The diagram illustrates the cellular edema process and the factors influencing it. Key processes include:

1. **Inhibition**
   - Out of the cell: $K^+$, $Na^+$
   - In the cell: ATP, ADP + Pi

2. **Acceleration**
   - Out of the cell: $H^+$, $Na^+$
   - In the cell: ATP

3. **Loss of membrane potential**
   - Out of the cell: $Ca^{++}$
   - In the cell: $Ca^{++}$, $O_2$

4. **Cellular edema**

5. **Key Changes**
   - $[Na^+]_i$ increases
   - $[H^+]_i$ increases
   - $[Ca^{++}]_i$ increases

6. **Side Effects**
   - Protein degradation
   - Protein structure modifications
   - Plasmic phospholipids degradation
   - Mitochondrial dysfunction

7. **Anaerobic metabolism**

The diagram also shows a decrease in oxygen ($O_2$) levels.
Role of pH

- Rapid correction of pH from acidic to normal pH results in intracellular Na$^+$ and Ca$^{2+}$ overloading
- Ischemic contracture/myocardial cell death
Intracellular Oedema

- Intracellular lactate, Na\(^+\) and Ca\(^{2+}\) accumulation
- Osmotic gradient created
- Cellular swelling occurs
- Disruptive to cytoskeleton
Oxidative Stress

- Reintroduction of oxygen leads to burst in reactive oxygen species (ROS)
- Overwhelms antioxidant proteins (catalase, superoxide dismutase, glutathione peroxidase)
- Widespread damage to enzymatic processes occurs
Mitochondrial Permeability Transition Pore (MPTP)

- Pore opening the terminal event in mitochondrial death
- Cell death ensues
Reperfusion injury during cardiac arrest

- Historically considered to occur at return of spontaneous circulation (ROSC)
- Increasingly recognized as occurring at initiation of chest compressions
Gradual/staged reperfusion studies from 1980-90s in dogs

Potential Clinical Implications

- Rapid correction of acidosis probably undesirable
- Sodium Bicarbonate potentially harmful
- High minute ventilations --> respiratory alkalosis potentially harmful
Ischemic Preconditioning

  - Decline in ATP halted after initial ischemic episode
  - Cells became more ischemia-tolerant
- Same effect seen via pharmacologic methods
  - Adenosine, diazoxide, volatile anesthetics

Robert B. Jennings
Ischemic Preconditioning

- Implications for sudden cardiac arrest research
  - Experimental animal models often use volatile anesthetics prearrest
- Human cardiac arrest
  - No clear therapeutic strategy
Ischemic Postconditioning of Myocardium in Dogs

Fig. 1. Experimental protocol used to determine the effect of one possible variation in ischemic postconditioning (Post-con) on myocardium after ischemia (I) and reperfusion (R). In the control group \((n = 10)\) there was no intervention; ischemic preconditioning (Pre-con, \(n = 9\)) was elicited by 5 min I followed by 10 min R before 60 min I; Post-con \((n = 10)\) was performed by 3 circles of 30 s of R followed by 30 s of I before 3 h of R, respectively.

Ischemic Postconditioning of Myocardium in Dogs

Fig. 2. Bar graph shows determination of infarct size by triphenyltetrazolium chloride (TTC) staining. Post-con significantly reduced area of necrosis (AN)-to-area at risk (AR) ratio by 48% compared with the control group, showing equivalent cardioprotection to that of Pre-con, *P < 0.05 vs. control. Values are group means ± SE.

Postconditioning the Brain

- Rat, mouse, and tree shrew models
- Global and focal ischemic models
  - Improved neurologic function/behavioral tests
  - Decreased apoptosis
- Postconditioning window fairly wide in this model
- Postconditioning 2 days after reperfusion reduced neuronal death in hippocampus with single 5 min episode of ischemia (Burda J, et al. Cell Mol Neurobiol 2006, 26:1141-51.)
Timing of Post-Conditioning for Myocardial Protection

- Delay in onset of >1 min abolishes effect in rat and rabbit cardiac models
- Number of postconditioning cycles
  - No apparent benefit to more than 3 cycles
- Duration of postconditioning episodes
  - 30 second pauses failed to show benefit on infarct size in swine and rat hearts while 10-20 seconds did

Ischemic Conditioning

- Introduction of intermittent ischemic insults to induce protection against ischemia/reperfusion
Ischemic Postconditioning

N. Segal et al. / Resuscitation 83 (2012) 1397–1403
Ischemic Postconditioning

N. Segal et al. / Resuscitation 83 (2012) 1397–1403

Cerebral Performance Category Score at 24 and 48 hours.

SCPR
SCPR + PC

§ $p < 0.0001$

* $p = 0.0034$

24 hours
48 hours
Areas of uncertainty

- Is postconditioning the same as staged/gradual reperfusion?
- Are the episodes of ischemia themselves protective...
- ...or are they effective as staged reperfusion...
- ...or both?
Cell Death and Survival Signals

Improves calcium homeostasis, reduces production of reactive oxygen species, increases production of nitric oxide, inhibits mPTP opening, and prevents apoptosis.

Bundled Therapy Targeting Multiple Pathways

- Targeting multiple biological pathways may be better than silver bullet
Bundled Therapy Experiment: Yannopoulos Lab

- Laboratory Investigation
  - Yorkshire Swine (N=20)
  - 38.6 + 0.4 kg
  - Anesthesia
    - Presedated with intramuscular ketamine
    - Intubated
    - General anesthesia with isoflurane 0.8-1.2 Vol%
    - Ventilated to target ETCO₂ 35-42 mm Hg
    - Room air FiO₂, supplemented as needed to SpO₂>95%

Presented as an oral abstract at ReSS 2013
Control Animals (n=8)
Bundled Postconditioning Therapy (n=12)

Presented as an oral abstract at ReSS 2013
Return of Spontaneous Circulation

Presented as an oral abstract at ReSS 2013
Ejection Fraction

Presented as an oral abstract at ReSS 2013
Biomarkers of end-organ damage 4-hr post ROSC

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Control</th>
<th>Bundle</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB</td>
<td>59.2 ±13.6</td>
<td>28.2 ±4.2</td>
</tr>
<tr>
<td>Troponon I</td>
<td>27.7 ±7.7</td>
<td>12.0 ±2.7</td>
</tr>
<tr>
<td>ALT</td>
<td>61.8 ±2.0</td>
<td>40.6 ±4.9</td>
</tr>
<tr>
<td>AST</td>
<td>258.3 ±67.3</td>
<td>124.6 ±24.0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.9 ±0.1</td>
<td>1.4 ±0.1</td>
</tr>
</tbody>
</table>

p<0.05 for all comparisons

Presented as an oral abstract at ReSS 2013
Adverse Events/Survival

- Status epilepticus
- Severe cardiopulmonary distress
- Deep coma

Presented as an oral abstract at ReSS 2013
Pharmacological activators of the RISK cardioprotective pathway

- Insulin
- Insulin-like growth factor-1
- atorvastatin
- bradykinin
- urocortin
- cardiotrophin 1
- transforming growth factor (TGF-β1)
- opioids

Postconditioning/Controlled Reperfusion

- No human data
  - Potential epidemiologic observations
    - Comparison of 30 compressions: 2 ventilations vs continuous compressions
What would postconditioning/controlled reperfusion trial look like?

- 911 Dispatch-assisted CPR ideal starting place
  - Inclusion:
    - Adult patients
    - Unwitnessed arrest
    - Bystander CPR not already started
Challenges

- Species specific differences in postconditioning timing/interval lengths
- Effects likely diminished by:
  - prolonged downtime = not enough salvageable tissue
  - etiology of arrest
  - age/comorbidities
- Creates complexity for prehospital providers
Guidelines

- Aside from therapeutic hypothermia, no currently recommended therapies to address reperfusion injury
- Should controlled pauses in CPR be recommended?
  - Human data needed
Summary

- Targeting reperfusion injury may benefit cardiac arrest victims
- Controlled reperfusion via structured pauses at the initiation of CPR most promising
- Additional pharmacological approaches worthy of exploration
- No single therapy likely to be silver bullet