The evolution of CPR and the era of post conditioning

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Disclosures

• Demetris Yannopoulos MD, is the Medical Director of the Minnesota Resuscitation Consortium, a state wide initiative to improve survival in the state of MN from cardiac arrest. This initiative is sponsored by the Medtronic Foundation and is part of the Heart Rescue Program.

• Dr. Yannopoulos is funded by an Institutional, Division of Cardiology grant at the University of Minnesota and an R01 HL108926-01 NIH grant for research in CPR, new technologies and pharmacological therapies.
Hypothesis

- We hypothesize that during CPR the initial intervention (CPR) can affect long term outcomes and improve resuscitation rates and survival.
- We believe that a “silver bullet”, single intervention does not exist during CPR.
- We therefore utilize a multi-prong approach that incorporates mechanical and pharmacological interventions. Our goal is to drastically increase CPR efficiency and protect from ischemia reperfusion injury during the initial minutes of resuscitation.
Sodium nitroprusside enhanced cardiopulmonary resuscitation improves survival with good neurological function in a porcine model of prolonged cardiac arrest*

Demetris Yannopoulos, MD; Timothy Matsuura, BS; Jason Schultz, MD; Kyle Rudser, PhD; Henry R. Halperin, MD; Keith G. Lurie, MD

**Objective:** To assess the effectiveness of sodium nitroprusside (SNP)-“enhanced” cardiopulmonary resuscitation (SNPeCPR) on 24-hr survival rates compared to standard CPR in animals after cardiac arrest. SNPeCPR consists of large intravenous SNP bolus doses during CPR enhanced by active compression-decompression CPR, an inspiratory impedance threshold device (ITD), and abdominal binding (AB). The combination of active compression-decompression CPR+ITD+AB without SNP will be called “enhanced” or eCPR.

**Design:** Randomized, blinded, animal study.

**Setting:** Preclinical animal laboratory.

**Subjects:** Twenty-four female farm pigs (30 ± 1 kg).

**Interventions:** Isoflurane anesthetized and intubated pigs were randomized after 8 mins of untreated ventricular fibrillation to receive either standard CPR (n = 8), SNPeCPR (n = 8), or eCPR (n = 8) for 25 mins followed by defibrillation.

**Measurements and Main Results:** The primary end point was carotid blood flow during CPR and 24-hr survival with good neurologic function defined as an overall performance category score of ≤2 (1 = normal, 5 = brain dead or dead). Secondary end points included hemodynamics and end-tidal CO₂. SNPeCPR significantly improved carotid blood flow and 24-hr survival rates with good neurologic function compared to standard CPR or eCPR (six of eight vs. zero of eight vs. one of eight, p < .05). The improved survival rates were associated with higher coronary perfusion pressure and ETCO₂ during CPR.

**Conclusion:** In pigs, SNPeCPR significantly improved hemodynamics, resuscitation rates, and 24-hr survival rates with good neurologic function after cardiac arrest when compared with standard CPR or eCPR alone. (Crit Care Med 2011; 39:1269–1274)

**Key Words:** vasodilators; cardiopulmonary resuscitation; neurological function; resuscitation rates; carotid blood flow
Prolonged CPR Hemodynamic study

8 min of untreated VF

25 min

SNPeCPR (8 animals)

S-CPR (8 animals)

“eCPR” NO SNP

(8 animals)

If ROSC

24-hour survival

Carotid Blood Flow (ml/min)

- SNPeCPR
- S-CPR + epi
- ACD CPR+ITD+AB

Baseline 5m 10m 15m 20m 25m

CPR
24 Hour Overall Performance Category Score

5 (dead)

* Good neurological outcomes

SNPeCPR  eCPR  S-CPR
Sodium nitroprusside-enhanced cardiopulmonary resuscitation improves resuscitation rates after prolonged untreated cardiac arrest in two porcine models*

Jason C. Schultz, MD; Nicolas Segal, MD; Emily Caldwell, RN; James Kolbeck, MD; Scott McKnite, BS; Nick Lebedoff, BS; Menekhem Zviman, PhD; Tom P. Aufderheide, MD; Demetris Yannopoulos, MD

**Objective:** Sodium nitroprusside-enhanced cardiopulmonary resuscitation consists of active compression-decompression, an impedance threshold device, abdominal binding, and large intravenous doses of sodium nitroprusside. We hypothesize that sodium nitroprusside-enhanced cardiopulmonary resuscitation will significantly increase carotid blood flow and return of spontaneous circulation compared to standard cardiopulmonary resuscitation after prolonged ventricular fibrillation and pulseless electrical activity cardiac arrest.

**Design:** Prospective randomized animal study.

**Setting:** Hennepin County Medical Center Animal Laboratory.

**Subjects:** Forty Yorkshire female farm-bred pigs weighing 32 ± 2 kg.

**Interventions:** In protocol A, 24 isoflurane-anesthetized pigs underwent 15 mins of untreated ventricular fibrillation and were subsequently randomized to receive standard cardiopulmonary resuscitation (n = 6), active compression-decompression cardiopulmonary resuscitation + impedance threshold device (n = 6), or sodium nitroprusside-enhanced cardiopulmonary resuscitation (n = 12) for up to 15 mins. First defibrillation was attempted at minute 6 of cardiopulmonary resuscitation. In protocol B, a separate group of 16 pigs underwent 10 mins of untreated ventricular fibrillation followed by 3 mins of chest compression only cardiopulmonary resuscitation followed by countershock-induced pulseless electrical activity, after which animals were randomized to standard cardiopulmonary resuscitation (n = 8) or sodium nitroprusside-enhanced cardiopulmonary resuscitation (n = 8).

**Measurements and Main Results:** The primary end point was carotid blood flow during cardiopulmonary resuscitation and return of spontaneous circulation. Secondary end points included end-tidal CO₂ as well as coronary and cerebral perfusion pressure. After prolonged untreated ventricular fibrillation, sodium nitroprusside-enhanced cardiopulmonary resuscitation demonstrated superior rates of return of spontaneous circulation when compared to standard cardiopulmonary resuscitation and active compression-decompression cardiopulmonary resuscitation + impedance threshold device (12 of 12, 0 of 6, and 0 of 6 respectively, p < .01). In animals with pulseless electrical activity, sodium nitroprusside-enhanced cardiopulmonary resuscitation increased return of spontaneous circulation rates when compared to standard cardiopulmonary resuscitation. In both groups, carotid blood flow, coronary perfusion pressure, cerebral perfusion pressure, and end-tidal CO₂ were increased with sodium nitroprusside-enhanced cardiopulmonary resuscitation.

**Conclusions:** In pigs, sodium nitroprusside-enhanced cardiopulmonary resuscitation significantly increased return of spontaneous circulation rates, as well as carotid blood flow and end-tidal CO₂, when compared to standard cardiopulmonary resuscitation or active compression-decompression cardiopulmonary resuscitation + impedance threshold device. (Crit Care Med 2011; 39:2705–2710)

**Key Words:** cardiopulmonary resuscitation; carotid blood flow; neurological function; resuscitation rates; vasodilators
Carotid Blood flow (ml/min)

- Baseline
- CCO-CPR
- ACLS INTERVENTION

SNPeCPR
S-CPR
End Tidal CO$_2$ (mmHg)

- Baseline
- CCO-CPR
- ACLS INTERVENTION

SNPeCPR vs S-CPR
<table>
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<tr>
<th></th>
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<th>CCO-CPR</th>
<th>SNPeCPR</th>
<th>1 hour ROSC</th>
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<tr>
<td><strong>SNPeCPR</strong></td>
<td></td>
<td></td>
<td></td>
<td>7/8</td>
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<tr>
<td><strong>ACLS Group</strong></td>
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<tr>
<td>SBP</td>
<td>111±9</td>
<td>42±10</td>
<td>85±13</td>
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<td>DBP</td>
<td>74±10</td>
<td>18±4</td>
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<tr>
<td>CPP</td>
<td>72±8</td>
<td>16±3</td>
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<tr>
<td>ICP</td>
<td>11±3</td>
<td>22±3</td>
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<tr>
<td>CerPP</td>
<td>82±8</td>
<td>8±4</td>
<td>36±5</td>
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<td><strong>S-CPR</strong></td>
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<td>SBP</td>
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<td>CerPP</td>
<td>76±9</td>
<td>10.5±3</td>
<td>17±3*</td>
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Sodium nitroprusside enhanced cardiopulmonary resuscitation prevents post-resuscitation left ventricular dysfunction and improves 24-hour survival and neurological function in a porcine model of prolonged untreated ventricular fibrillation

Jason Schultz a, Nicolas Segal a, James Kolbeck a, Emily Caldwell a, Marit Thorsgard a, Scott McKnite a, Tom P. Aufderheide b, Keith G. Lurie a, Demetris Yannopoulos a, *

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ABSTRACT

Aim of study: Sodium nitroprusside-enhanced CPR, or SNP-CPR, consists of active compression-decompression CPR with an impedance threshold device, abdominal compression, and intravenous sodium nitroprusside (SNP). We hypothesize that SNP-CPR will improve post resuscitation left ventricular function and neurological function compared to standard (S) CPR after 15 min of untreated ventricular fibrillation in a porcine model of cardiac arrest.

Methods: Pigs (n = 22) anesthetized with isoflurane underwent 15 min of untreated ventricular fibrillation, were then randomized to 6 min of S-CPR (n = 11) or SNP-CPR (n = 11) followed by defibrillation. The primary endpoints were neurologic function as measured by cerebral performance category (CPC) score and left ventricular ejection fraction.

Results: SNP-CPR increased 24-hour survival rates compared to S-CPR (10/11 versus 5/11, p = 0.03) and improved neurological function (CPC score 2.5 ± 1, versus 3.8 ± 0.4, respectively, p = 0.004). Left ventricular ejection fractions at 1, 4 and 24 hours after defibrillation were 72 ± 11, 57 ± 11.4 and 64 ± 11 with SNP-CPR versus 29 ± 10, 30 ± 17 and 39 ± 6 with S-CPR, respectively (p < 0.01 for all).

Conclusions: In this pig model, after 15 min of untreated ventricular fibrillation, SNP-CPR significantly improved 24-hour survival rates, neurologic function and prevented post-resuscitation left ventricular dysfunction compared to S-CPR.
15 min of untreated VF
Protocol Timeline

SNPeCPR
(11 animals)

Epi 0.5 mg if NO ROSC after 3 shocks

Total of 15 min of CPR; if no ROSC END of study

If ROSC 24 hour observation

(Epi 0.5 mg)

S-CPR
(11 animals)

2 mg (11 animals)

1 mg

6 min
Left Ventricular Function in SNPeCPR vs S-CPR

* Significant difference
Overall Performance Score Category

<table>
<thead>
<tr>
<th>5 or dead</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
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- **SNPeCPR**
- **Standard CPR**

Good neurological outcome
Figure 1. Contribution of Lethal Reperfusion Injury to Final Myocardial Infarct Size.

**Myocardial ischemia in absence of reperfusion**
Infarct size, 70%

**Myocardial ischemia with reperfusion**
Reperfusion reduces infarct size by 40%.
Part of the remaining 30% infarct is due to lethal reperfusion injury and is therefore preventable.

**Myocardial ischemia with reperfusion and cardioprotection**
Preventing lethal reperfusion injury reduces infarct size by a further 25%, realizing the full benefits of reperfusion.
MECHANISMS OF DISEASE

Myocardial Reperfusion Injury

Derek M. Yellon, D.Sc., and Derek J. Hausenloy, Ph.D.

CORONARY HEART DISEASE IS THE LEADING CAUSE OF DEATH WORLDWIDE, and 3.8 million men and 3.4 million women die of the disease each year. After an acute myocardial infarction, early and successful myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) is the most effective strategy for reducing the size of a myocardial infarct and improving the clinical outcome. The process of restoring blood flow to the ischemic myocardium, however, can induce injury. This phenomenon, termed myocardial reperfusion injury, can paradoxically reduce the beneficial effects of myocardial reperfusion.

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Figure 3. New Cardioprotective Strategies for Reducing Lethal Reperfusion Injury.

For patients with an acute myocardial infarction, ischemic postconditioning or pharmacologic agents that activate the reperfusion injury salvage kinase (RISK) pathway or inhibit the opening of the mitochondrial permeability transition pore (PTP), or a multitargeted pharmacologic approach before or during the immediate onset of myocardial reperfusion, may attenuate lethal reperfusion injury and reduce the final myocardial infarct size.
<table>
<thead>
<tr>
<th>Cardioprotective Strategy and Source</th>
<th>No. of Patients</th>
<th>Period of Ischemia, hr</th>
<th>Timing of Intervention</th>
<th>Details of Study</th>
<th>Clinical End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic postconditioning</td>
<td></td>
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<tr>
<td>Staat et al.</td>
<td>30</td>
<td>5.5</td>
<td>During PCI</td>
<td>Four 60-sec low-pressure inflations and deflations of coronary-angioplasty balloon immediately after stent deployment</td>
<td>Reduced infarct size by 36% and improved myocardial reperfusion</td>
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<tr>
<td>Latkey</td>
<td>17</td>
<td>5.7</td>
<td>During PCI</td>
<td>One 90-sec inflation and deflation of coronary-angioplasty balloon immediately after stent deployment</td>
<td>Improved ST-segment resolution and coronary blood flow</td>
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<td>Ma et al.</td>
<td>94</td>
<td>7</td>
<td>During PCI</td>
<td>Three 30-sec low-pressure inflations and deflations of coronary-angioplasty balloon immediately after stent deployment</td>
<td>Reduced infarct size, improved wall-motion score index, increased myocardial reperfusion, and improved endothelial function</td>
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<td>Atrial natriuretic peptide</td>
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<td>Kitakaze et al.</td>
<td>569</td>
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<td>Before PCI</td>
<td>Intravenous infusion</td>
<td>Reduced infarct size by 15%, improved LVEF by 5%, and improved myocardial reperfusion, but no effect on mortality; reduced composite end point of cardiac death and cardiac failure</td>
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<td>Protein kinase C-delta inhibitor (KAI-9803)</td>
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<td>Intracoronary bolus of KAI-9803</td>
<td>Reduced infarct size and improved ST-segment resolution</td>
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<td>Roe</td>
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<td>Before PCI</td>
<td>Intravenous glucagon-like peptide 1 given to patients with poor LVEF</td>
<td>Improved LVEF from 29% to 39%</td>
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<td>Nikolaidis et al.</td>
<td>21</td>
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<td>Intravenous bolus of darbepoetin alfa</td>
<td>Mobilized endothelial progenitor cells but no effect on left ventricular function</td>
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<td>Darbepoetin alfa (a long-acting erythropoietin analogue)</td>
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<td>Intravenous bolus of darbepoetin alfa</td>
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<td>Remote ischemic postconditioning</td>
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<td>Before PCI</td>
<td>Remote ischemic postconditioning using transient upper-limb ischemia</td>
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<tr>
<td>Atorvastatin</td>
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<td>Before PCI</td>
<td>High-dose atorvastatin administered 12 hr before PCI</td>
<td>Reduced myocardial injury during PCI</td>
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<td>Mitochondrial PTP inhibition</td>
<td></td>
<td></td>
<td>Before PCI</td>
<td>Intravenous bolus of cyclosporine</td>
<td>In progress</td>
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</table>
Ischemic Postconditioning Protects Against Global Cerebral Ischemia/Reperfusion-Induced Injury in Rats

Jing-ye Wang, MD; Jia Shen, MS; Qin Gao, PhD; Zhi-guo Ye, MS; Shui-you Yang, BS; Hua-wei Liang, PhD; Iain C. Bruce, PhD; Ben-yan Luo, MD; Qiang Xia, PhD

Background and Purpose—Ischemic postconditioning has been found to decrease brain infarct area and spinal cord ischemic injury. In this study, we tested the hypothesis that ischemic postconditioning reduces global cerebral ischemia/reperfusion-induced structural and functional injury in rats.

Methods—Ten-minute global ischemia was induced by 4-vessel occlusion in male Sprague-Dawley rats. The animals underwent postconditioning consisting of 3 cycles of 15-second/15-second (Post-15/15), 30-second/30-second (Post-30/30), or 60-second/15-second (Post-60/15) reperfusion/reocclusion or 15-second/15-second reperfusion/reocclusion applied after a 45-second reperfusion (Post-45/15/15).

Results—Ten minutes of ischemia and 7 days of reperfusion destroyed 85.8% of CA1 hippocampal neurons and 64.1% of parietal cortical neurons. Three cycles of Post-15/15, Post-30/30, and Post-45-15/15 reperfusion/reocclusion markedly reduced neuronal loss after 7 days or 3 weeks of reperfusion and diminished the deficiency in spatial learning and memory. After reperfusion, a period of hyperperfusion followed by hypoperfusion was observed, both of which were blocked by postconditioning. The cytosolic level of cytochrome c increased significantly after 48 hours of reperfusion, and this was inhibited by Post-15/15, Post-30/30, and Post-45-15/15. However, 3 cycles of 60-second/15-second reperfusion/reocclusion failed to protect against neuronal damage, behavioral deficit, or cytochrome c translocation.

Conclusions—Our data provide the first evidence that an appropriate ischemic postconditioning strategy has neuroprotective effects against global cerebral ischemia/reperfusion injury and a consequent behavioral deficit and that these protective effects are associated with its ability to improve disturbed cerebral blood flow and prevent cytochrome c translocation. (Stroke. 2008;39:983-990.)
• Short duration pauses during reperfusion protect the heart from AMI
• Protect the brain from ischemic cell death after global ischemia and focal stroke.
• The same concept has been verified in all organs (liver, kidney, small intestine and retina).
• ....
• Doesn’t that sound suitable as a therapy after prolonged cardiac arrest?
Ischemic Post-conditioning (IPC) putting the .... dots TOGETHER!

• The AHA recommends immediate and continuous compressions at first contact with the patient with cardiac arrest regardless of the time of untreated ischemia.

• Ischemic PC: “stutter” or “controlled” reperfusion
  – short pauses of CPR may provide benefit
  – Cyclosporin A may provide benefit
  – Adenosine may provide some protection

• Prolonged repetitive pauses in CPR have been associated with bad outcomes due to bad cardiac perfusion and brain perfusion.

• We hypothesize that 3-4 cycles of 20sec on/off CPR followed by good quality CPR can provide IPC without adversely affecting cardiac resuscitation and would protect heart and brain from I/R injury therefore improving outcomes.
Controlled pauses at the initiation of sodium nitroprusside-enhanced cardiopulmonary resuscitation facilitate neurological and cardiac recovery after 15 minutes of untreated ventricular fibrillation

Demetris Yannopoulos, MD; Nicolas Segal, MD; Scott McKnite, BS; Tom P. Aufderheide, MD; Keith G. Lurie, MD

Objective: A multipronged approach to improve vital organ perfusion during cardiopulmonary resuscitation that includes sodium nitroprusside, active compression-decompression cardiopulmonary resuscitation, an impedance threshold device, and abdominal pressure (sodium nitroprusside-enhanced cardiopulmonary resuscitation) has been recently shown to increase coronary and cerebral perfusion pressures and higher rates of return of spontaneous circulation vs. standard cardiopulmonary resuscitation. To further reduce reperfusion injury during sodium nitroprusside-enhanced cardiopulmonary resuscitation, we investigated the addition of adenosine and four 20-sec controlled pauses spread throughout the first 3 mins of sodium nitroprusside-enhanced cardiopulmonary resuscitation. The primary study end point was 24-hr survival with favorable neurologic function after 15 mins of untreated ventricular fibrillation.

Design: Randomized, prospective, blinded animal investigation.

Setting: Preclinical animal laboratory.

Subjects: Thirty-two female pigs (four groups of eight) 32 ± 2 kg.

Interventions: After 15 mins of untreated ventricular fibrillation, isoflurane-anesthetized pigs received 5 mins of either standard cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine, or controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine. After 4 mins of cardiopulmonary resuscitation, all animals received epinephrine (0.5 mg) and a defibrillation shock 1 min later. Sodium nitroprusside-enhanced cardiopulmonary resuscitation-treated animals received sodium nitroprusside (2 mg) after 1 min of cardiopulmonary resuscitation and 1 mg after 3 mins of cardiopulmonary resuscitation. After 1 min of sodium nitroprusside-enhanced cardiopulmonary resuscitation, adenosine (24 mg) was administered in two groups.

Measurements and Main Results: A veterinarian blinded to the treatment assigned a cerebral performance category score of 1–5 (normal, slightly disabled, severely disabled but conscious, vegetative state, or dead, respectively) 24 hrs after return of spontaneous circulation. Sodium nitroprusside-enhanced cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine, and controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine resulted in a significantly higher 24-hr survival rate compared to standard cardiopulmonary resuscitation (7 of 8, 8 of 8, and 8 of 8 vs. 2 of 8, respectively p < .05). The mean cerebral performance category scores for standard cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation, sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine, or controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine were 4.6 ± 0.7, 3 ± 1.3, 2.5 ± 0.9, and 1.5 ± 0.9, respectively (p < .01 for controlled pauses-sodium nitroprusside-enhanced cardiopulmonary resuscitation + adenosine compared to all other groups).

Conclusions: Reducing reperfusion injury and maximizing circulation during cardiopulmonary resuscitation significantly improved functional neurologic recovery after 15 mins of untreated ventricular fibrillation. These results suggest that brain resuscitation after prolonged cardiac arrest is possible with novel, noninvasive approaches focused on reversing the mechanisms of tissue injury. (Crit Care Med 2012; 40:000–000)

Key Words: active compression-decompression cardiopulmonary resuscitation; adenosine; cardiopulmonary resuscitation; impedance threshold device; left ventricular function; neurological function; reperfusion injury; sodium nitroprusside; survival
Fig. 1  Standard CPR with ischemic postconditioning (SCPR+PC) protocol

Pause 20sec  Pause 20sec  Pause 20sec  Pause 20sec
CPR 40sec  CPR 20sec  CPR 20sec  CPR 20sec
CPR  ROSC

15 minutes of untreated VF

Aortic pressure tracing (mmHg)

0.5 mg of Epinephrine

ROSC

Yannopoulos D. et al. JACC under review
Fig. 2  Cerebral Performance Category Score at 24 and 48 hours.

* $ p = 0.0034$

§ $ p < 0.0001$

SCPR

SCPR + PC

24 hours

48 hours
Cerebral Performance Category of 4 (severe neurological dysfunction, coma)

Ischemic neurons
* 3 animals that survived to 24 hours with CPC of 4 (coma). Samples collected at 24 hours!

48-hour survival (CPC <3)

* p=0.040
Does the method of CPR matter during IPC?

Fig. 2 Cerebral Performance Category Score

SCPR with IPC

Superior CPR method with IPC

YES!
Summary re: Reperfusion and Ischemic Injury

There are 3 mechanisms of injury that contribute to overall neurological function after 15 min of untreated VF.

1) Ischemic injury from the untreated VF itself (systemic absence of FLOW) :
   not much we can do! Treat as fast as possible.

2) Reperfusion injury from blood flow reintroduction at the initiation of CPR:
   reduced by ‘stutter’ CPR and cyclosporine A (maybe SNP and adenosine)

3) CPR related ischemic injury due to the inability of the CPR method to meet the metabolic requirements of the vital organs (not enough flow) as the CPR efforts are prolonged:
   reduced by good quality CPR, ACD+ITD CPR,
   vasodilators (SNP and adenosine)
Conclusions

• New approaches to improving flow to vital organs and to decreasing reperfusion injury may well significantly improve outcomes after cardiac arrest in the future.
• These novel approaches will be tested in humans within the next 1-2 years
• Stay tuned!
• In the meantime, we should focus on improving quality of CPR early delivery of therapy to the patients and improving circulation to the heart and brain.
• The ITD (currently available) and the ACD CPR + ITD (Under FDA review) should be strongly considered and combined in a strong systems-based-approach to cardiac arrest.
• These technologies may be the mechanical foundation of a whole new approach to CPR.