**Does it Work?**

**Standard vs. ACD CPR:**

<table>
<thead>
<tr>
<th>Human Study</th>
<th>Survival</th>
<th>Standard or ACD CPR during ACLS only</th>
</tr>
</thead>
</table>

Odds ratios shown above bars.

* Statistically significant difference

**Standard vs. ACD CPR:**

<table>
<thead>
<tr>
<th>Human Study</th>
<th>Survival</th>
<th>Standard or ACD CPR during BLS and ACLS</th>
</tr>
</thead>
</table>

Odds ratios shown above bars.

* Statistically significant difference

**Does it Work?**
ACD CPR

What's the problem?

Inefficiency #2

- Air rushes in through an open airway and wipes out the vacuum we're relying on to fill the heart.
- Heart stops filling as soon as vacuum is equalized.

The Solution

- The Impedence Threshold Device (ITD)
ACD/ITD CPR in humans

Plaisance, P, Lurie, KG, Payen, D. Circ. 2000;101:989-994

Human Study

Diastolic Arterial Pressure (mm Hg)

Duration of CPR (minutes)

Without Valve

With Valve

n=11

n=10

n=10

n=10

n=9

n=8

n=10

n=8

n=10

n=7

n=8

n=8

n=7

n=8

n=7

n=8

n=7
Sudden Cardiac Arrest Prevention and Treatment: Strengthening the Chain of Survival

ACD CPR +/- Valve: Coronary Perfusion Pressure

Paris Survival Study: ACD CPR ± ITD

- Prehospital study
- 200 patients/arm (ACD vs. ACD/ITD)
- ROSC:
  - 38.5% - ACD
  - 48% - ACD/ITV
- ICU admission:
  - 28.5% - ACD
  - 39.5% - ACD/ITV
- 24 Hour Survival:
  - 22% - ACD
  - 32% - ACD/ITV

Plaisance, P, Lurie, KG, Payen, D. Circ. 2000;101:989-994

Human Study

THE LANCET

"Cardiopulmonary resuscitation with augmentation of negative intrathoracic pressure should be considered as an alternative to standard CPR to increase long-term survival after cardiac arrest."
Comparative Effects of Standard CPR Versus Active Compression Decompression CPR with Augmentation of Negative Intrathoracic Pressure for Treatment of Out-of-Hospital Cardiac Arrest: Results from a Randomized Prospective Study

Tom P. Aufderheide, MD; Ralph J. Frascone, MD; Marvin A. Wayne, MD; Brian D. Mahoney, MD; Robert A. Swor, DO; Robert M. Doremus-Fitz, MD; Michael L. Olinger, MD; Richard G. Holcomb, PhD; David E. Tupper, PhD; Demetris Yannopoulos, MD; Keith G. Lurie, MD

Methods

- S-CPR (Control)
- ITD + ACD-CPR (Intervention)

Hypothesis

Survival to hospital discharge with favorable neurologic function (measured with a modified Rankin Scale [mRS] ≤ 3), is higher in patients receiving an ITD + ACD-CPR compared to patients receiving Standard CPR (S-CPR).
Methods:

Study Design

- Prospective, randomized, controlled clinical trial with data analyzed on intent to treat basis
- Seven US sites (population base: 2.3 million):
  - 46 EMS agencies
  - 4350 EMS providers
  - 25 IRBs
- Patients assigned, based upon weekly block randomization, to control or intervention group
- Study period: February 2005 – July 2010
- All study personnel blinded to aggregate data

Results:

Primary Endpoint

Survival to Hospital Discharge with Favorable Neurologic Outcome

*53% improvement

\[ P = 0.019 \]

OR 1.58

CI (1.07, 2.36)

Consistency Across Age Groups

Survival to Hospital Discharge with Favorable Neurologic Outcome

<table>
<thead>
<tr>
<th>Age at Time of Arrest (years)</th>
<th>Control (n = 47)</th>
<th>Intervention (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;29</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>30-39</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>40-49</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>50-59</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>60-69</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>70-79</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>&gt;79</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Results: Consistency Across Genders

Control (n = 833)  
Intervention (n = 840)

P = 1.00 for differences based on gender
Odds ratio for effect of intervention based on gender: 1.60  
95% CI (1.10, 2.33)

Survival to Hospital Discharge with Favorable Neurologic Outcome

<table>
<thead>
<tr>
<th>Gender</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: Consistent Benefit Throughout Enrollment

Survival to Hospital Discharge with Favorable Neurologic Outcome

<table>
<thead>
<tr>
<th>Quarter</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: One-year Survival

<table>
<thead>
<tr>
<th></th>
<th>Control (N = 813)</th>
<th>Intervention (N = 840)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-Year Survival</td>
<td>48 (5.9%)</td>
<td>74 (8.8%)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Control Mean ± SD</th>
<th>Intervention Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional</td>
<td>5.2 ± 6.3</td>
<td>5.5 ± 5.9</td>
<td>0.862</td>
</tr>
<tr>
<td>Functional</td>
<td>1.4 ± 3.1</td>
<td>2.2 ± 5.7</td>
<td>0.358</td>
</tr>
<tr>
<td>Cognitive</td>
<td>92.9 ± 12.0</td>
<td>94.5 ± 4.5</td>
<td>0.473</td>
</tr>
</tbody>
</table>
Compared to standard CPR, ITD + ACD-CPR resulted in significantly increased survival to hospital discharge with favorable neurological function (53%).

One year after OOHCA, survival rates with similar neurologic function were also significantly higher in the intervention group (49%).

Purpose

To determine if use of an active (versus sham) ITD during standard CPR (no ACD used) would improve rates of hospital discharge with functional neurological survival in adult (modified Rankin Scale [mRS] score ≤3), non-traumatic, out of hospital cardiac arrests.
Description/Methods

- 10 sites in US and Canada
- Prospective, randomized, blinded
- Subjects: adults with arrest from presumed cardiac etiology
  - Analyze Early (30 secs CPR) vs Analyze Later (3 min CPR)
    - Stiell et al. NEJM 2011
    - Sham vs Active ITD
    - Aufderheide et al. NEJM 2011
- Impact of immediate CPR feedback utilizing QCPR device @ three sites
  - Hostler et al. BJM 2011

Results

- Overall results in sham vs active ITD were similar (≈6%)
- November 2, 2009, NIH announced study terminated early (at the 2/3 enrollment point) as it was not going to be possible to detect any overall significant difference between either of the study groups (AnE vs AnL, or sham vs active ITD) even if study continued to 14,000 patients (stopped because of futility)
- No safety concerns with ITD

Conclusion

- Compared with standard CPR, use of the ITD did not significantly improve functional survival from out-of-hospital cardiac arrest.
- When implemented under similar conditions, routine use of the ITD is not supported.
Protocols

• Three different BLS protocols
• ALS protocols per site medical director

Various ROC Study Protocols

<table>
<thead>
<tr>
<th>Protocols</th>
<th>Sites Participating</th>
</tr>
</thead>
<tbody>
<tr>
<td>30:2 compression to ventilation ratio</td>
<td>Milwaukee, WI, Dallas, TX, San Diego, CA, Portland, OR, Birmingham, AL, Ottawa, CA, Toronto, CA</td>
</tr>
<tr>
<td>Sham vs Active ITD</td>
<td>Pittsburgh, PA, Thunder Bay, ON</td>
</tr>
<tr>
<td>Continuous chest compressions with asynchronous ventilation @ 100s</td>
<td>Vancouver, CA, Seattle (King County), WA</td>
</tr>
</tbody>
</table>

Study Protocol

Respond to scene and determine pulselessness.
Perform 1 – 4 simultaneously:
1. Review enrollment criteria for AE vs AL study
   a) If eligible and in V-Fib, perform either 30 secs or 3 min of CPR prior to analyzing and shocking if indicated.
   b) If eligible and in asystole or PEA, or not eligible, perform conventional resuscitation
2. Review enrollment criteria for QCPR study
   a) If eligible, place QCPR device; then, based upon cluster randomization, audible and visual feedback either will or will not be given to rescuers.
   b) If not eligible, do not place QCPR device and perform conventional resuscitation.
3. Review enrollment criteria for ITD study
   a) If eligible, select ITD in serialized order and place on patient.
   b) If not eligible, perform conventional resuscitation.
4. Perform other conventional activities of resuscitation (e.g. airway management, IV/IO, administer medications, defibrillate)
Complexity

“There were different enrollment criteria for the different studies, so once we got to the scene and determined that the patient was in cardiac arrest, we determined what rhythm they were in. If they were in V-fib, we had to review the enrollment criteria again and do 30 seconds of CPR before shock if indicated. We then needed to place and shock ifindicated. We also remembered to place the QCPR device between our hands and the patient’s sternum – sometimes we got real feedback and sometimes we didn’t. We also had to then review the enrollment criteria for the ITD study and decide whether to place an ITD in a randomized order. If they were in asystole or PEA, we did the same thing except without the 30 secs or 3 min of CPR first. All of this, in addition to everything else we do on cardiac arrests, and on calls we do less than 5% of the time.”

- Paramedic comment on ROC study methodology (paraphrased) -

**ROC ITD Placement Intervals**

**The Devil is in the Details**

<table>
<thead>
<tr>
<th>Time Intervals (minutes)</th>
<th>First/BLS Response</th>
<th>ALS Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dispatch to first unit arrival</td>
<td>5.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Arrival of rig carrying ITD to application</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Time from 911 call to dispatch of EMS (estimated)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Estimated mean ITD placement interval</td>
<td>10.8 minutes</td>
<td>14.0 minutes</td>
</tr>
</tbody>
</table>

**Device Placement Intervals**

**ROC PRIMED Study**

<table>
<thead>
<tr>
<th>Median Time Intervals (minutes)</th>
<th>First/BLS Response</th>
<th>ALS Response</th>
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<tr>
<td>Dispatch to first unit arrival</td>
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**ResQTrial Study**

<table>
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<tr>
<th>Mean Time Intervals (minutes)</th>
<th>EMS Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>911 call to EMS CPR start time</td>
<td>6.7</td>
</tr>
<tr>
<td>Time it took EMS to place devices once CPR begun</td>
<td>0.4 (24 secs)</td>
</tr>
<tr>
<td>911 call to device placement</td>
<td>7.1 min</td>
</tr>
</tbody>
</table>
Problems

- Complicated Analyze Early vs Analyze Later & QCPR protocols, multivariate design caused multiple problems:
  - ITD placement was very delayed (up to 14 minutes)
  - Almost 40% of cases did not have ITD placed within the planned time interval (under 5 minutes)
  - All the patients who survived in under approximately 4 minutes were not eligible for the ITD
  - Essentially all cases of early use were on asystolic patients
- Treatment protocols were all over the place

3-Phase Model of Resuscitation

Comparison of Device Placement Times: ResQtrial vs ROC Study
The Bottom Line

- 2 very different studies
  - ITD
  - ACD/ITD
- Early survivors were excluded from getting the ITD (under 4 minutes)
- ITD was used early on probable, non-survivors (asystole)
- ITD way too late for the device to be successful

ResQ Trial CPR Quality

High overall survival rates in the control group (9.8%) were consistent with high quality S-CPR and twice that reported in ROC trial.
Multi-Level Focus and Translational Effort

- Widespread CPR Training (e.g., CPR Anytime)
- AEDs
- Public Education

Survival

- Rapid Response
- Start CPR Immediately
- Rapid AED Application
- High Quality CPR
- ITD (ResQPOD)

Reperfusion Centers of Excellence
- Hypothermia
- 24/7 Revascularization
- ICDs

- High Quality CPR
- IO drug delivery prn
- ITD (e.g., ResQPOD)
- Automated CPR Devices (LUCAS)

Multi-Level Focus and Translational Effort

Take Heart St. Cloud and Anoka Outcomes (AHA Nov 08)

- From 2006-2007 in the two MN sites
  - >12,000 people were trained in CPR,
  - Bystander CPR rates increased by ~5%,
  - All CPR interventions and the ResQPOD deployed,
  - Three Level One Cardiac Arrest Centers were established.

- Survival to hospital discharge for all patients following OHCA in these two sites improved from 8.5% (9/107) (historical control) to 19% (47/247) (intervention phase) (p = 0.011, OR 2.56, CI 1.17, 6.17)
The Evolution of CPR

The FUTURE
Current Research
Dimitrius Yanopoulous MD
Keith Lurie MD
Nicholas Seagal MD

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 Nipride "enhanced" CPR (SNPeCPR)
• ACD+ITD (Improved short and long term outcomes in 5 clinical studies)
• Sodium Nitroprusside (the most potent vasodilator with predominant arterial effect and NO donor) (SNP)
Prolonged untreated VF and SNPeCPR
Pushing the limits of Resuscitation Science

15 minutes of untreated VF followed by 6 minutes of SNPeCPR before defibrillation effort versus S-CPR with epinephrine q3 minutes per the 2010 AHA guidelines

Yannopoulos D, et al 2011
In press, Critical Care Medicine

AHA 2010

SNPeCPR + 2 mg SNP
1 mg SNP
0.5 mg Epi

15 minutes of untreated VF followed by SNPeCPR

One shock ROSC
15min of VF

Protocol Timeline

SNP
SNPeCPR
(11 animals)
2 mg SNP
1 mg SNP
0.5 mg Epi

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

If ROSC 24 hour observation

15 min of untreated VF

S-CPR
(11 animals)
3-Phase Model of Resuscitation

- **Myocardial ATP**
- **Electrical Phase**
- **Circulatory Phase**
- **Metabolic Phase**

**Arrest Time (min)**: 0, 4, 10, 20

Weisfeldt ML et al. JAMA 2002:288:3035-8

Left Ventricular Function in SNPeCPR vs S-CPR

- **Left Ventricular Ejection Fraction, %**
- **1 hour**, **4 hours**, **24 hours**

*SNPeCPR*, **Control**

Overall Performance Score Category

- **1**
- **2**
- **3**
- **4**
- **5 or dead**

**Good** neurological outcome