The Circulation Improving Resuscitation Care (CIRC) Trial

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Conflict of Interest

- Dr. Herken employed by ZOLL Medical Corp.
- Trial funded by ZOLL
  - ZOLL and Principal investigator developed the trial protocol with
    - Study investigators
    - Staff at Data Coordinating Center
    - Statistical consultants
- Investigators’ institutions received funding from ZOLL
Mechanical Chest Compression

• May overcome poor compression quality
• Advantages
  – Reduces provider fatigue
  – Can be used in confined spaces
  – Safely deliver compressions during transport
  – Can be used during interventions
  – Bridge to more advanced procedures
Mechanisms for Creating Blood Flow during CPR
The Load Distributing Band uses both sternal and thoracic pump mechanisms to create blood flow during CPR
Statistics for dummies

- We perform a study in a small part of the world and talk about our results as it was the world we had studied.

- The world probability is \( p \), but the probability we have found is \( p^* \).

- We need a measure to visualize how much these probabilities diverge.

- A Confidence Interval (CI) describe how much \( p^* \) (an estimate of a probability) diverge from \( p \) (the true probability).
Statistics for dummies

• Mean is a reasonable estimate (however, uncertain) for expectation of something we would like to know

• If we create an interval around mean that with great probability will include our expected value it will be our CI and will be a measure of the uncertainty of mean

• The smaller the CI is, the more reliable is our results in reflecting the real world
Statistics for dummies

• Odds – is possibilities, (deutch: chancen)
  – ratio

• Confidence – believe in, (deutch: vertrauen, norwegian: tillit)
  – interval
  – It measure the margin of error of a measure and is reported as %.
  – A 95% CI include the true value with a probability of 0.95.
Study Device

- Load Distributing Band
- Battery powered
- Reduces AP chest diameter by 20%
- 30:2 or continuous compressions
- Rate 80 min⁻¹
AutoPulse/LDB Research

• Shown to improve hemodynamics*
• Pre-hospital survival studies conflict
  – 3 retrospective studies found improved outcome ‡
  – 1 RCT (ASPIRE) stopped early#
    • No difference in 4 hour survival
    • Cerebral performance worse at discharge

*Ikeno F 2006; Duchateau FX 2010; Timerman 2004; Halperin 2004
‡Casner 2005; Ong 2006; Krep 2007;
#Hallstrom 2006
CPR fraction

Chest compressions

Start CPR

End CPR

Total CPR time is 10 min, chest compressions for 5 min
CPR fraction is 50%
CIRC Trial Objectives

• Compare iA-CPR vs. M-CPR
  – Primary endpoint:
    • Survival to hospital discharge
  – Secondary endpoints:
    • ROSC to ED
    • 24 hour survival
  – Safety endpoint:
    • mRS score
Clinical paper

Design of the Circulation Improving Resuscitation Care (CIRC) Trial: A new state of the art design for out-of-hospital cardiac arrest research

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l Department of Anesthesiology, Division of Emergency Medicine, University of Erlangen, Erlangen, Germany

Simulation and education

Advanced life support performance with manual and mechanical chest compressions in a randomized, multicentre manikin study

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d Department of Mathematics and Natural Sciences, University of Stavanger, Norway
e Houston Fire Department, Houston, TX, USA
f Department of Surgery, Baylor College of Medicine, Houston, TX, USA
g ZOLL Medical Corporation, Chelmsford, MA, USA
Setting

The Fox Valley Region, WI

Vienna, Austria

Houston, TX

Hillsborough County, FL

Nijmegen, The Netherlands
PI Trial Requirements

1. High quality manual CPR

2. Monitor CPR process in both arms

3. Standardized training
Provider training

- 4 hour standardized training
  - Review study protocol
  - Review CPR process
  - Pit Crew deployment strategy
  - Written and practical examination
Verification of Protocol Adherence

• Formal simulation study*
  – Full Megacode simulation
  – Validation of protocol and training program
• Evaluated protocol compliance
• Evaluated CPR quality
  – AutoPulse AND manual compressions
• Used to guide refresher training curriculum

*Tømte Ø et al Resuscitation 2009
Trial Phases

• Three distinct study phases

- **In-Field Phase**
  Deployment and usage of the AutoPulse for every OHCA*

- **Run-In Phase**
  Randomization and adherence to full study protocol for each OHCA*

- **Statistical Inclusion**
  Randomization and adherence to full study protocol for each OHCA – Data included in analysis

*Transition based on predefined measures of protocol compliance according to monitoring of the CPR process
Subject Inclusion

- 18 years of age or older
- OHCA of presumed cardiac etiology
- Randomization after M-CPR initiated
Randomization Procedure

- Confirm cardiac arrest
- Verify need for CPR
- Start manual compressions
- Determine trial eligibility
- Open randomization envelope
- Treat per randomization card
Subject Exclusion

- Known or apparent pregnancy
- Do Not Resuscitate orders
- Too big for the AutoPulse
- Prisoner or ward of the state
- Prior application of a mechanical chest compression device
- Randomizing EMS unit arrived ≥16 minutes after emergency call
Determination of Inclusion/Exclusion

- Best estimate of EMS providers
  - No treatment delay
- Some cases excluded after enrollment
  - Except for patient size
  - Retrospective exclusion monitored by DSMB
Data Analysis

• Group Sequential Double Triangular Test

• Powered to determine superiority, inferiority, or equivalence
  – Two-sided significance level 5%
  – Power 97.5%

• Equivalence defined as OR 95%
  CI fully between 0.69 and 1.44
Vil bruk av AutoPulse ved hjertetans utenfor sykehus øke hands-off tiden?

Jan-Åge Olsen, MD og PhD-stipendiat, Nasjonalt Kompetansesenter for Prehospital Akuttmedisin (NAKOS), Oslo Universitetssykehus og Universitetet i Oslo, Institutt for klinisk medisin
Impedanse

• En kjent høyfrekvent, lav amplitude, vekselstrøm blir sendt gjennom brystkassen mellom defibrillator-padsene.

• Resulterer i spenning gjennom brystkassen som måles vha Ohms lov

• Ved hjelp av prosessering og programvare kan man få frem kurver som analyseres
Zoll RescueNet Code Review™ (utvikler-versjon)
Bruk av elektroniske defibrillatordata

- Physio-Control defibrillatorer: Bruk av transthorakal impedanse validert for kompresjoner.\(^1\) Ikke for ventilasjoner under pågående kompresjoner.\(^2\)
- Zoll defibrillatorer bruker impedanse for å tolke ventilasjoner og akselerometer-data for kompresjoner


CIRC
AutoPulse® Clinical Trial
Metode

• En annoteringsalgoritme ble utviklet for en enhetlig tilnærming. Denne basert på tidligere erfaring\(^1\) og publiserte metoder for å analysere elektroniske data.

• Pause i kompresjoner definert som mer enn 1.5 sekunder mellom to kompresjoner.\(^2\)


Metode, forts.

• Kontinuerlig EKG og akselerometer- eller impedanse data ble analyser for å bestemme
  – Antall kompresjoner per minutt
  – Antall ventilasjoner per minutt
  – Tiden det tok før Autopulse var i bruk i iA-HLR-armen
  – Antall sjokk
  – Om det ble defibrillert gjennom kompresjoner

• Defibrillering gjennom kompresjoner – minst 50% av defibrilleringene måtte skje mens Autopulse komprimerte
Metode, forts.

• HLR-fraksjon ble regnet ut for de første 5, 10 og 20 minuttene
• Deskriptiv statistikk og 95% konfidensintervall ble beregnet
Tid fra siste manuelle kompresjon til første Autopulse-kompresjon

14 sekunder

x1.0, 25 mm
Sjokk under pågående HLR

Sjokk gis
Autopulse startes etter sjokket
Kontinuerlig Autopulse

En litt lenger pause mellom 2 kompresjoner slik at man får ventilert.
Autopulse, 30:2
### Resultater

<table>
<thead>
<tr>
<th>Tid fra defibrillator på til første registrerte kompresjon (sekunder)</th>
<th>M-HLR (n=2024)</th>
<th>iA-HLR (n=2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>61 ± 127</td>
<td>65 ± 139</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HLR-fraksjon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ved 10 minutter</td>
</tr>
<tr>
<td>Ved 20 minutter</td>
</tr>
</tbody>
</table>

| Antall kompresjoner per minutt første 10 minutter | 89,2 ± 17,4 | 66,3 ± 10,7 |

| Antall ventilasjoner per minutt første 10 minutter | 8,8 ± 4,7 | 6,8 ± 3,4 |

Elektroniske data tilgjengelig for 96% av episodene
Resultater

<table>
<thead>
<tr>
<th></th>
<th>M-HLR (n=2024)</th>
<th>iA-HLR (n=2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defibrillerte pasienter (%)</td>
<td>40%</td>
<td>38%</td>
</tr>
<tr>
<td>Median antall defibrilleringer i episoder med defibrillering</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

- Median tid fra siste manuelle kompresjon til første Autopulse-kompresjon 29 sekunder (IQR 17-43)
- I 74% av iA-HLR episodene ble det sjokket gjennom kontinuerlig kompresjoner
### Diskusjon

<table>
<thead>
<tr>
<th></th>
<th>HLR-fraksjon, 5 min</th>
<th>HLR-fraksjon, 10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ong, Manuell arm¹</td>
<td>72% ± 20%</td>
<td>69%</td>
</tr>
<tr>
<td>CIRC Manuell arm⁰</td>
<td>79,0% ± 12,3%</td>
<td>79,7% ± 10,1%</td>
</tr>
<tr>
<td>Ong, LDB arm¹</td>
<td>60% ± 20%</td>
<td>69,5%</td>
</tr>
<tr>
<td>CIRC iA-HLR⁰</td>
<td>74,7 ± 12,7%</td>
<td>78,5% ± 9,4%</td>
</tr>
</tbody>
</table>

¹HLR-fraksjon for første 20 minutter

Begrensninger elektroniske data

• Ingen kompresjonsdybde fra elektroniske data fra Physio-Controls maskiner

• Bare analysert første 20 minutter av episodene for HLR-fraksjon (10 minutter for ventilasjoner)
Problemområder

- Svært mye manuelt arbeid. Softwaren brukt i denne studien er fortsatt under utvikling
- Estimert 10 millioner museklikk bare for selve annoteringene.
- Anta 1 museklikk per sekund: Man vil sitte og klikke i 115 dager (dag og natt)
Takk til

• Lars Wik (hovedveileder)
• Petter Andreas Steen (biveileder)
Results

• 9,068 calls with presumed cardiac arrest
  – 4315 excluded at time of EMS response:
    • 3467 No CPR attempted (Dead On Arrival - DOA)
    • 245 Non-cardiac etiology
    • 275 Met exclusion criteria
    • 328 Missed enrollment
  – 522 excluded post enrollment
    • 10.4% M-CPR
    • 11.0% iA-CPR

• 4,231 included subjects
  • 50.4% (2132) M-CPR
  • 49.6% (2099) iA-CPR
## General Characteristics by Arm

<table>
<thead>
<tr>
<th></th>
<th>M-CPR n=2132</th>
<th>iA-CPR n=2099</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>65.6 ± 16.0</td>
<td>65.7 ± 16.4</td>
</tr>
<tr>
<td><strong>Male gender</strong></td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>Public location of OHCA</strong></td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Bystander witnessed</strong></td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Bystander CPR</strong></td>
<td>49%</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Shockable initial rhythm</strong></td>
<td>24%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Response interval [min]</strong></td>
<td>6.6 ± 3.0</td>
<td>6.7 ± 2.9</td>
</tr>
<tr>
<td><strong>Prehospital epinephrine</strong></td>
<td>91%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Hospital hypothermia</strong></td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>PTCA/ PCI</strong></td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Time from arrival to termination/transport [min]</strong></td>
<td>36.1 ± 14.1</td>
<td>37.3 ± 14.3</td>
</tr>
<tr>
<td><strong>Initial rhythm VF/ VT average time from defib on to first shock [min]</strong></td>
<td>3.5 ± 4.0</td>
<td>4.6 ± 4.8</td>
</tr>
<tr>
<td><strong>Time from defib on to first recorded compression(s)</strong></td>
<td>61 ± 127</td>
<td>65 ± 139</td>
</tr>
</tbody>
</table>

*calculated based on total included in the arm
Results: Adverse Events

• Medical monitor received 34 adverse event reports
  – 28 were determined to be unexpected
  – 26 of those were serious

• DSMB reviewed all 34 cases
  – No new risks identified
  – No safety concerns
Results: Effectiveness Endpoint

• Equivalent survival to hospital discharge
  – Primary Endpoint
  – OR 1.06, 95% CI 0.83 - 1.37
    • Adjusted for covariates (age, witnessed arrest, initial cardiac rhythm, and enrollment site) and interim analysis
    • Within pre-defined equivalence region (0.69 - 1.44)
## Results: Effectiveness Endpoint

<table>
<thead>
<tr>
<th></th>
<th>M-CPR (n=2132)</th>
<th>iA-CPR (n=2099)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival to Hospital Discharge</strong></td>
<td>11.0%</td>
<td>9.4%</td>
<td>0.84 (0.69 – 1.02)</td>
<td>1.06 (0.83 - 1.37)</td>
</tr>
<tr>
<td><strong>Survival to 24h</strong></td>
<td>25.0%</td>
<td>21.8%</td>
<td>0.84 (0.72 – 0.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Sustained ROSC Survival to ED</strong></td>
<td>32.3%</td>
<td>28.6%</td>
<td>0.84 (0.74 – 0.96)</td>
<td></td>
</tr>
</tbody>
</table>
Results: Safety Endpoint

- No difference in mRS scores ≤3
  - Adjusted OR 0.80, 95% CI 0.47 - 1.37 (n.s.)

<table>
<thead>
<tr>
<th></th>
<th>M-CPR (n=233)</th>
<th>iA-CPR (n=196)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge mRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score of 0 -3</td>
<td>48.1%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Score of 4 -5</td>
<td>26.2%</td>
<td>25.5%</td>
</tr>
<tr>
<td>Unknown score</td>
<td>25.8%</td>
<td>30.1%</td>
</tr>
</tbody>
</table>
Subgroup Analysis
Subgroup Analysis

• Witnessed Arrests with VF/VT
• Survival higher for iA-CPR if CPR fraction <80%
• No survival difference with higher CPR fractions.
• Example: CPR fraction 70% OR 3.4, 95% CI 2–7.4

CIRC
AutoPulse® Clinical Trial
Discussion - Methods

• Three study phases
  • Consistent study practices

• Training and compliance monitoring
  • High CPR fraction in both arms
  • High overall survival rate (10.2%)

• Patient level randomization
  • Equivalent subject characteristics

• Good patient tracking
  – 98% cases with digital ECG data files
  – 12 cases missing primary endpoint data
Discussion - Results

• Equivalence
  – Study powered to show true statistical equivalence.
  – At least as good as high-quality M-CPR

• iA-CPR may solve practical problems
  – CPR in confined spaces
  – CPR with limited number of rescuers
  – CPR during transport
Discussion - Results

- CPR fraction
  - ~80% CPR Fraction in both arms
    - Higher than most CPR fractions reported for other large RCTs.
  - High CPR fraction hard to achieve and maintain
  - Sub-analysis demonstrated that at more typical “clinical” CPR fractions iA-CPR may be better than M-CPR
CPR Fraction Predicts Survival

- The Resuscitation Outcomes Consortium (ROC) reports the CPR Fraction to independently predict survival in cardiac arrest patients.

- CPR Fraction was employed as the primary marker of CPR quality during the CIRC trial.

Limitations

• Post-resuscitation care not standardized
• Clock Synchronization
• CPR fraction only quality measure
• Arrival at patient side same defibrillator on
Conclusions

• CPR quality was good for both groups
• It is possible to achieve High quality manual CPR that saves lives
• Compared to high quality M-CPR:
  – iA-CPR resulted in statistically equivalent survival to hospital discharge
  – No difference in neurologic status at discharge