Mild Therapeutic Hypothermia
And Myocardial Recovery
Following Sudden Cardiac Death

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Chain of Survival for SCA

- Four critical links to emphasize
  - Early access to emergency care
  - Early CPR / CCC
  - Early defibrillation
  - Early ACLS

- Each link is effected by the preceding
Sustained “Untreated VF”

6:02 A.M.

6:05

6:07

6:11
The Problem

• OOH cardiac arrest:
  “Sudden and unexpected pulseless condition attributable to cessation of cardiac mechanical activity”

• Wide variation in incidence / outcomes:
  – Differences in definition
  – Limitation of ascertainment of SCA data
  – Disparity in treatment
Norwegian swimming champion Alexander Dale Oen dies

Norwegian swimming champion Alexander Dale Oen has died in the US, aged 26, Norway's swimming federation says.

He was found collapsed in a shower late on Monday after training in Flagstaff, Arizona, Norwegian media say. Officials said he had suffered a cardiac arrest.

Emergency services arrived at the scene within minutes but were unable to revive him.

Dale Oen won gold in the 100m breaststroke at the World Championships in Shanghai in July 2011.
Magnitude of SCA in the US

- Stroke\(^3\): 167,366
- Lung Cancer\(^2\): 157,400
- Breast Cancer\(^2\): 40,600
- AIDS\(^1\): 42,156

SCA claims more lives each year than these other diseases combined.

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\(^3\) *2002 Heart and Stroke Statistical Update*, American Heart Association.
\(^4\) *Circulation*. 2001;104:2158-2163.
DEFIBRILLATION SUCCESS
Depends on Speed of Application

After the first minute, success decreases 7-10% for each minute of delay

Circulation 1991:83:1832
Casino AED Programs
Defibrillation by Security Officers

**Survival**

Collapse-Shock <3min
74%*

Collapse-Shock >3min
49%*

*P=0.02

UA CPR research group,
*NEJM* 2000
- Treatment for VF is defibrillation
- Defib success is **time-dependent**
  - ~100% ROSC if immediate defibrillation
  - Decreases by 7-10% per minute
- Bystander CPR improves outcome
  - Increases odds ratio of survival by 2-4X
Prolonged VF is different

- Myocardial bioenergetics deteriorate with prolonged VF
- VF waveforms deteriorate
  - Coarse → fine (road to ‘smarter AED’s)
- Defib 1st after prolonged VF usually results in a non-perfusing rhythm
- Most pre-hospital VF is prolonged
VF Survival in Seattle after AEDs

Cobb, JAMA 1999
CPR 1\textsuperscript{st} vs Defib 1\textsuperscript{st} Seattle Observational Study

- No improvement in CPR with AEDs despite 3-4 minute decrease in time to delivery of shocks
- L. Cobb noted that \textit{prompt CPR was emphasized less with AEDs}
- Changed Seattle EMT protocol: Prompt CPR for 90 secs prior to AED
Survival to Hospital Discharge

Percent Survival to Hospital Discharge

- Shock First: 24%
- CC First: 30%

OR = 1.42
p = 0.04

Cobb, JAMA 1999
ROSC after 1\textsuperscript{st} shock(s)

\begin{itemize}
\item \textbf{CPR 1\textsuperscript{st}} \hspace{1cm} \textbf{Defib 1\textsuperscript{st}}
\item 9/15* \hspace{1cm} 0/15*
\end{itemize}

* P<0.001
CPR 1\textsuperscript{st} vs. Defib 1\textsuperscript{st}
Oslo RCT- OOH VF

200 adults randomized

1. Defibrillation 1\textsuperscript{st}
   \[N = 96\]

2. CPR 1\textsuperscript{st}: 3 minutes of CPR, then shock
   \[N = 104\]

Wik L, \textit{et al.} \textit{JAMA} 2003
### CPR vs. Defib First

#### > 5 minutes response time:

<table>
<thead>
<tr>
<th></th>
<th>ROSC</th>
<th>Hosp D/C</th>
<th>1 Yr Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Defib:</strong></td>
<td>38%  (21/55)</td>
<td>4%  (2/55)</td>
<td>4%  (2/55)</td>
</tr>
<tr>
<td><strong>CPR:</strong></td>
<td>58%  (37/64)</td>
<td>22%  (14/64)</td>
<td>20%  (13/64)</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.22</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>7.42</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>6.76</td>
<td>.01</td>
</tr>
</tbody>
</table>

Wik L, *et al.* *JAMA* 2003; 289:1389-95
3 phases of VF

• **Electrical (≤ 4min)**
  – Immediate defibrillation

• **Circulatory (>4-10min)**
  – Pre-shock chest compressions usually needed
  – *Post-shock CC may also be valuable

• **Metabolic (10-15min)**


New Dogma

- **Electrical Phase**
  - Defibrillate
  ~0-4 minutes

- **Circulatory Phase**
  - CPR 1st
  ~4-10 minutes

- **Metabolic Phase**
  - Hypothermia, ?drugs
  >10 minutes

Weisfeldt, Becker, JAMA 2002
"Electrical Phase"
Response time < 4 min

"Circulatory Phase"
Response time > 4 min

Cobb, JAMA 1999
Hemodynamic Shifts Following Cardiac Arrest

- Sinus Rhythm
- VF
- Prolonged VF
- PEA
- CCC
- Sinus
Approach to the problem – a basic, clinical, and translational program

- **Basic Program**: determine small v large animal
  - Importance of animal skills / veterinary staff

- **Clinical Program**: work within local resources
  - Identifying current understanding of problem

- **Translational Approach**: value of imaging
  - Increases collaboration across groups (bidirectional)
Open chest vs Closed chest

• **Pericardial and chest wall restraint**
  – Slow rate of RV filling
  – Decrease amount of RV filling
  – Greater effect on LV volume because of ventricular interdependence

• **Measure actual ventricular volumes**
  – Echo - limited 3D delineation (swine)
  – MRI – unable to ‘gate’ ECG in VF rhythm
Atrial function

bronchoatrial coronary anastomotic flow
Cardiac MRI

- Highly sophisticated imaging tool
- No RADIATION
- No IODINATED CONTRAST
- Reference standard for size, EF, mass
  - Cost-saving tool due to higher accuracy

*Able to identify areas of scarring*
Continuous Cardiac Magnetic Resonance Imaging During Untreated Ventricular Fibrillation
Vincent L. Sorrell, Maria I. Altbach, Karl B. Kern, Scott Squire, Ronald W. Hilwig, Melinda M. Hayes, Gordon A. Ewy and Robert A. Berg

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Continuous Cardiac Magnetic Resonance Imaging During Untreated Ventricular Fibrillation
Vincent L. Sorrell, MD; Maria I. Altbach, PhD; Karl B. Kern, MD; Scott Squire, AS; Ronald W. Hilwig, DVM, PhD; Melinda M. Hayes, MD; Gordon A. Ewy, MD; Robert A. Berg, MD

Cardiac magnetic resonance imaging (CMR) was performed in 6 swine after the induction of ventricular fibrillation (VF). With use of a 1.5-T GE Sigma NV-CV/i scanner (GE Medical Systems), data were acquired with a steady-state, free-precession pulse sequence (repetition time=3.7 ms, echo time=1.6 ms, α=45°, matrix=224×224, field of view=36×27 cm², slice thickness=6 mm, slice gap=0 mm). During VF, the pulse sequence was set to acquire untagged data (ie, data at a single cardiac phase). Data collection started immediately after the initiation of VF and continued every 30 seconds for 30 minutes. Images were analyzed offline (CMR Tools), and the comprehensive volumetric data were published in Circulation as a companion article (Circulation. 2005;111:1136–1140). The midcardiac slice from 1 swine is graphically displayed as a time-elapsed image (Figure and corresponding Movie). This provides an immediate visual appreciation of the right and left ventricular response to VF that is consistent with the volumetric data presented in the companion article. In this close chest, intact-pericardium swine model of untreated VF, the evolution from immediate right ventricular dilation (first minute) to early left ventricular dilation and wall thinning (5 minutes) and finally left ventricular ischemic contracture (“stone” heart at 20 to 30 minutes) was consistently seen in all 6 animals.
Single-phase, ungated, steady-state, free-precession CMR short-axis images acquired consecutively during 30 minutes of untreated VF are displayed over time.

Sorrell V L et al. Circulation 2005;111:e294-e294
Time elapsed: 30min/5s

Sorrell V L et al. Circulation 2005;111:e294-e294
Magnetic Resonance Imaging During Ventricular Fibrillation Reveals Prompt Right Ventricular Overdistention Without Left Ventricular Enlargement

Robert A. Berg, MD, FCCM; Vincent L. Sorrell, MD; Ronald W. Hilwig, DVM, PhD; Maria I. Altbach, PhD; Kathryn A. Bates, DO; Gordon A. Ewy

Background—Most out-of-hospital ventricular fibrillation (VF) is prolonged and results in asystole or pulseless electrical activity. An open-chest, open-pericardium model of swine VF indicates that blood flows into the right ventricle, thereby overdistending the ventricle.

Methods and Results—Ventricular dimensions were determined by MRI for a closed-pericardium model in 6 swine. Within 1 minute of untreated VF, the right ventricle overdistended but did not increase thereafter. The first 5 minutes of untreated VF resulted in 34% between 20 and 30 minutes of untreated VF, stone heart occurred as manifest by septal thinning and concomitant substantial decreases in left ventricular volume.

Conclusions—In this closed-chest swine model of VF, substantial right ventricular overdistention does not result in smaller left ventricular volumes. The changes in ventricular volumes do not explain why defibrillation from brief duration VF (<5 min) results in spontaneous circulation, whereas defibrillation from prolonged VF (>10 to 12 min) does not.

Key Words: cardiopulmonary resuscitation – heart arrest – hemodynamics – magnetic resonance imaging – ventricular fibrillation

<table>
<thead>
<tr>
<th>Time, min</th>
<th>RV Volume, mL</th>
<th>LV Volume, mL</th>
<th>Septum Width, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>39±4</td>
<td>52±3</td>
<td>6.6±0.6</td>
</tr>
<tr>
<td>0.5</td>
<td>51±5</td>
<td>40±5</td>
<td>7.4±0.5</td>
</tr>
<tr>
<td>1</td>
<td>66±6</td>
<td>42±3*</td>
<td>7.0±0.2</td>
</tr>
<tr>
<td>10</td>
<td>65±4*</td>
<td>47±3*</td>
<td>5.3±0.4*</td>
</tr>
<tr>
<td>15</td>
<td>65±3*</td>
<td>47±2*</td>
<td>5.6±0.4*</td>
</tr>
<tr>
<td>20</td>
<td>62±3*</td>
<td>46±2</td>
<td>5.7±0.2*</td>
</tr>
<tr>
<td>25</td>
<td>59±3*</td>
<td>33±7</td>
<td>7.6±0.8</td>
</tr>
<tr>
<td>30</td>
<td>51±2</td>
<td>12±1*</td>
<td>11.7±0.3*</td>
</tr>
</tbody>
</table>

NSR indicates normal sinus rhythm; EDV, end-diasstolic volume; ESV, end-systolic volumes; time 0 time when VF was induced; and times 0.5 through 30 minutes of untreated VF. All values are mean±SEM.

*Volume or width differs from that at time 0; P<0.05.
Time course of relative RV and LV volumes during 30’ VF

7 minutes sustained VF
High fidelity micromanometer-tipped catheters
Time course of mean AO and RA pressure
Mean volumes from current work overlaid
Cardiac magnetic resonance imaging investigation of sustained ventricular fibrillation in a swine model—With a focus on the electrical phase


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\# Department of Pediatrics, Soner Heart Center, University of Arizona, Tucson, AZ 85724-5073, United States

Sorrell V L et al. Resuscitation 2007;73:279
Mid LV slice = 3D volumes

Sorrell V L et al. Resuscitation 2007;73:279
Figure 4 Scatter plot of the left ventricular data used in the regression analysis. The 10 data points, representing the various durations of VF shown in Figure 3, are very close to the regression line and provide a confirmation of the goodness of fit ($r^2 > 0.95$). The two points with very small volumes and areas represent the development of LV stone heart.

Figure 5 Scatter plot of the right ventricular data used in the regression analysis. The 10 data points, representing the various durations of VF shown in Figure 3, are very close to the regression line and provide a confirmation of the goodness of fit ($r^2 > 0.95$).
“Stone Heart”


Stone Heart

• LV Ischemic Contracture
  – Described in 1960s and 1970s
    • After cross-clamping aorta for CABGs
  – Associated with ↓ high-energy phosphates
    • Presumed to be energy failure

• Prevention
  – Hypothermia
  – Asystolic arrest
  – Cardioplegic solutions
Historical Perspective

“Among 201 patients dying ... after cardiac surgery... and studied at autopsy [& postmortem coronary arteriography]... there were 4 (2%) with stone heart syndrome. All had undergone aortic valve surgery for aortic stenosis employing hypothermic anoxic arrest. At the conclusion of an uncomplicated operation, the heart was firm, contracted, prone to fibrillate, and could not sustain the circulation.”

“Pathological study showed widely patent coronary arteries and severe contraction band necrosis of the inner portions of both ventricular walls.”

“The stone heart syndrome appears to be simply the manifestations produced by massive contraction band necrosis in a severely hypertrophied heart.”

Myocardial Contracture

FIG. 4. Left ventricular diastolic pressure and wall thickness during ischemic cardiac arrest. Diastolic pressure was measured at Vp, wall thickness was measured with LV balloon empty (Vp). After 60 min of ischemic arrest, a progressive increase in chamber stiffness (diastolic pressure at Vp) was associated with increased LV wall thickness. Asterisk indicates that LV diastolic pressure was greater than 100 mmHg; see text.

Presumed limit of resuscitability

• No reports of recovery from “stone heart”
• No ability to perfuse myocardium due to microcirculatory collapse from tetanic systolic contraction
• Manual massage (Cooley) does not obtain CO

Presumed limit of resuscitability

• N=36; aggressive attempts at resuscitation
• “Firm myocardium”
  – “very firm”: never resumed contractile activity
  – “less firm (not soft)”: some return of contractile activity (albeit insufficient)
• Authors noted this was “mainly in the LV”

Limit of Resuscitibility

• Open-chest (O) cardiac massage
  – Option when closed-chest (C) fails
  – Uncertain if beneficial after 15-20+ minutes VF

• N=20 dogs; VF duration, O vs C, CPP
  – 10-20’ VF: ROSC 5/5 O & C
  – >20’ VF: ROSC 5/5 O (CPP 58mmHg)
  – >20’ VF: ROSC 1/5 C (CPP 2mmHg)
  – >40’ VF: ROSC 0/0 O & C

Quick Summary

• 3 phases of sustained VF
• EMS arrives during circulatory phase
• Prompt CPR/CCC prior to defib is beneficial
• CMR re-defined the 3 phases in a closed-chest model
• Old dogma of “early LV compression” is wrong
• A final, inevitable late phase = stone heart
• Once reached, this is the “limit of resuscitability”

“A stone let go cannot be recalled”
Peter Safar, MD
University of Pittsburgh
1961

Figure 1. Heart-lung resuscitation (cardiopulmonary-cerebral resuscitation). First composition in 1961, Pittsburgh, PA. Reproduced with permission from Safar, P. Community-wide CPR. J Iowa Medical Society 1964 (Nov); pp 629-635.
Post-arrest Mild Hypothermia Saves Lives
Hypothermia – just for CNS?

• Since 1950’s to mitigate neurological injury
• Mild (32-34): 2 RCT’s demonstrate post-VF value
  – Focused on neuro-protection
  – ? Cardio-protective?

• Mod (28-32), deep (<28) profound (<15)
  – Reduce neuronal / myocardial O2 need
  – Increase VF risk / coagulopathy / infection
Hypothermia: Cardioprotective

• Improved VF defibrillation success after persistent VF (8 min) if mild hypothermia

• Beneficial effect of hypothermia was not due to
  – alteration of coronary perfusion pressure
  – suggests change in the mechanical, metabolic, or electrophysiological properties of the myocardium

• Hypothermia *reduces ATP depletion* during ischemia resulting in less mitochondrial dysfunction and increased functional recovery of heart

Boddicker KA, (Kerber) et al. Circ 2005, 111: 3195-201
Mild hypothermia delays the development of stone heart from untreated sustained ventricular fibrillation—a cardiovascular magnetic resonance study

Vincent L. Sorrell1,2,*, Vijayasekhar Paliu1, Maria I Altbach2, Ronald W. Hilwig2, Karl B. Kern1, Mohamed Gaballa1, Gordon A. Ewy1, Robert A. Berg1

Abstract

Background: ‘Stone heart’ resulting from ischemic contracture of the myocardium, precludes successful resuscitation from ventricular fibrillation (VF). We hypothesized that mild hypothermia might slow the progression to stone heart.

Methods: Fourteen swine (77 ± 1 kg) were randomized to normothermia (group I, n = 8) or hypothermia groups (group II, n = 6). Mild hypothermia (34 ± 2°C) was induced with ice packs prior to VF induction. The LV and right ventricular (RV) cross-sectional areas were followed by cardiovascular magnetic resonance until the development of stone heart. A commercial 1.5T GE Signa NV-CVI scanner was used. Complete anatomic coverage of the heart was acquired using a steady-state free precession (SSFP) pulse sequence gated at baseline prior to VF onset. Un-gated SSFP images were obtained serially after VF induction. The ventricular endocardium was manually traced and LV and RV volumes were calculated at each time point.

Results: In group I, the LV was dilated compared to baseline at 5 minutes after VF and this remained for 20 minutes. Stone heart, arbitrarily defined as LV volume ≤1/3 of baseline at the onset of VF, occurred at 20 ± 3 minutes. In group II, there was less early dilation of the LV (p < 0.05) and the development of stone heart was delayed to 52 ± 4 minutes after onset of VF (p < 0.001).

Conclusions: In this closed-chest swine model of prolonged untreated VF, hypothermia reduced the early LV dilatation and importantly, delayed the onset of stone heart thereby extending a known, morphologic limit of resusciatability.

Table 1

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Hypothermia (n = 6)</th>
<th>Normothermia (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LV (ml)</td>
<td>RV (ml)</td>
</tr>
<tr>
<td>0</td>
<td>40 ± 3</td>
<td>46 ± 3</td>
</tr>
<tr>
<td>5</td>
<td>45 ± 3</td>
<td>62 ± 5</td>
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<td>46 ± 4</td>
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<td>55</td>
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<td>34 ± 6</td>
</tr>
<tr>
<td>60</td>
<td>12 ± 2</td>
<td>34 ± 4</td>
</tr>
</tbody>
</table>

Changes in ventricular dimensions during normal sinus rhythm and during VF in both normothermia and mild hypothermia groups. Data are mean ± SE, *p < 0.05 hypothermia vs normothermia.
Prolong “Limit of Resuscitability”

Intra-arrest cooling

- Hypothermia facilitates resuscitation
- Refractory VF may allow time for rapid hypo
- External cooling not practical
- Novel devices
How does hypothermia protect?

- **Unknown! (ask Circ, Circ Res, JACC, NEJM, etc)**
- **Hypothesis: “attenuates ischemic injury”**
  - Direct relationship between temp and ATP decay
    - Prolongs time for ATP loss to reach ‘energy limit of resusc’
    - Delays reduction of pH (slows onset to marked acidosis)
- **Variable effects on Defib thresholds (not strictly EP)**
- **Benefit of cardioplegia was intensified with hypo**
  - iNOS activity is decreased (less myo / cerebral ischemic injury)
How does hypothermia protect?

• Unknown!
• Hypothesis: “attenuates ischemic injury”
  – Direct relationship between temp and ATP decay
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• Variable effects on Defib thresholds (not strictly EP)
• Benefit of cardioplegia was intensified with hypo
  – iNOS activity is decreased (less myo / cerebral ischemic injury)
Hypothermia: cardioprotective

• Brain injury (rat) model
• Inducible NO synthase (iNOS) activity contributes to myo / brain ischemic injury
• Hypothermia decreases early and late iNOS
• Hypothermia attenuates iNOS mRNA and iNOS protein production, induced myocardial expression of cytokines IL 10 and 4
• *If hypothermia has myocardial effects similar to effects in the brain*, cardioprotective effect would be more clear

Sustained untreated VF

6:02 A.M.

6:05

6:07

6:11

4 MINUTES

8 MINUTES
Future Investigations

• Control hypothermia in MR scanner
• *Does CPR alter these findings*
• Does intra-arrest hypothermia have similar effect
• *Can we perform LV biopsies during stone*
• *What happens during the electrical phase if higher temporal resolution is applied*
Conclusions

• Persistent untreated VF = 3 phases
• Rapid RV / LV dilation is blunted with hypothermia
• Stone Heart = limit of resuscitability
• Hypothermia delays this limit
• Imaging has rapidly advanced our understanding of this entity and alerted us to misconceptions
• A new paradigm is born: Hypothermia has “cardioprotective” as well as “neurocognitive” benefit

_A scientific man ought to have no wishes, no affections – a mere heart of stone (C. Darwin 1859)_