Seneca

• **CONDITION:** Anthracycline induced cardiomyopathy

• **PI:** Jay Traverse, MD

• **CONTACT INFO:** Jane Fox | Jane.Fox@allina.com | 612-863-6289

• **DESCRIPTION:** Safety and feasibility study of delivering investigational allogeneic human mesenchymal stem cells (allo-MSCs) via NOGA to cancer survivors with left ventricular (LV) dysfunction secondary to anthracycline-induced cardiomyopathy (AIC).

• **CRITERIA LIST/ QUALIFICATIONS:**
  - Cancer survivor with diagnosis of Anthracycline induced cardiomyopathy.
  - Have an LVEF ≤ 40% by cMRI.
  - NYHA class II-III.
  - Previous myocardial infarction is exclusionary.

• **SPONSOR:** National Institutes of Health/The University of Texas Health Science Center (CCTRN Data Coordinating Center)
The MRC initiatives for VF/VT and OHCA. Redefining Acute Cardiac Care and Resuscitation.

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Robert K Eddy Endowed Chair for Cardiovascular Resuscitation
Medical Director, Minnesota Resuscitation Consortium
Division of Cardiovascular Medicine
University of Minnesota

Disclosures

• Dr. Yannopoulos is funded by the NIH Grants for CPR and resuscitation research.
  – 2013 Transformative Research NIH Director’s Award 1R01HL123227-05 (PI)
  – R01 HL108926-05 (PI)
  – R01 HL133818-01 (PI) the ACCESS trial
  – R01HL126092-02 (co-Investigator)
  – R01HL122323-02 (co-Investigator)

Dr Yannopoulos has received funding from the Helmsley Charitable Trust to transform emergent care for cardiac arrest patients in the state of MN.
Early Access to the Cardiac Catheterization Laboratory for Patients Resuscitated From Cardiac Arrest Due to a Shockable Rhythm: The Minnesota Resuscitation Consortium Twin Cities Unified Protocol

Santiago Garcia, MD; Todd Drewel, MD; Wobo Beknelwers, MD; Ganesh Revrendran, MD; Emily Caldwell, RN; Lucinda Holgorsen, BA, EMT-P; Qi Wang, MS; Selouk Adabag, MD; Brian Mamoney, MD; Ralph Frascona, MD; Gregory Halmer, MD; Charles Liek, MD; Marc Contrasto, MD; Kenneth Ilarre, MD; Bradley Bart, MD; Fouad Bouhour, MD; Steven Roh, MD; Carmelo Panetta, MD; Randall Stari, MD; Mark Houstian, MD; Michael Moorey, MD; Keith Wesley, MD; Demetrio Yannopolous, MD

Background—In 2013 the Minnesota Resuscitation Consortium developed an organized approach for the management of patients resuscitated from shockable rhythms to gain early access to the cardiac catheterization laboratory (CCL) in the metro area of Minneapolis-St. Paul.

Methods and Results—Eleven hospitals with 24/7 percutaneous coronary intervention capabilities agreed to provide early (within 6 hours of arrival at the Emergency Department) access to the CCL with the intention to perform coronary revascularization for outpatients who were successfully resuscitated from ventricular fibrillation/ventricular tachycardia arrest. Other inclusion criteria were age >18 and ≤76 and presumed cardiac etiology. Patients with other rhythms, known do not resuscitate/do not intubate, noncardiac etiology, significant bleeding, and terminal disease were excluded. The primary outcome was survival to hospital discharge with favorable neurological outcome. Patients (315 out of 331) who were resuscitated from VT/VF and transferred alive to the Emergency Department had complete medical records. Of these, 231 (73.3%) were taken to the CCL per the Minnesota Resuscitation Consortium protocol while 84 (26.6%) were not taken to the CCL (protocol deviations). Overall, 197 (63%) patients survived to hospital discharge with good neurological outcome (Cerebral Performance Category of 1 or 2). Of the patients who followed the Minnesota Resuscitation Consortium protocol, 12 (52%) underwent percutaneous coronary intervention, and 15 (7%) underwent coronary artery bypass graft. In this group, 15 (65%) survived with good neurological outcome, whereas in the group that did not follow the Minnesota Resuscitation Consortium protocol, 46 (35%) survived with good neurological outcome (adjusted odds ratio: 1.99; 95% CI: 0.71-5.32, P=0.03).

Conclusions—Early access to the CCL after cardiac arrest due to a shockable rhythm in a selected group of patients is feasible in a large metropolitan area in the United States and is associated with a 65% survival rate to hospital discharge with a good neurological outcome. (J Am Heart Assoc. 2016;5:e002670. doi: 10.1161/JAHA.115.002670)
### Table 3. Survival to Hospital Discharge With Favorable Neurological Outcomes

<table>
<thead>
<tr>
<th>Overall Population Outcomes</th>
<th>MRC Protocol (N=230)</th>
<th>Protocol Deviations (N=64)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged alive</td>
<td>227 (72%)</td>
<td>170 (74%)</td>
<td>1.31 (1.77, 2.27)</td>
<td>0.32</td>
<td>1.60 (0.83, 3.10)</td>
<td>0.16</td>
</tr>
<tr>
<td>CPC 1 or 2</td>
<td>197 (63%)</td>
<td>151 (65%)</td>
<td>1.58 (0.94, 2.60)</td>
<td>0.09</td>
<td>1.09 (1.07, 3.72)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No ST-Elevation Population Outcomes</th>
<th>MRC Protocol (N=211)</th>
<th>Protocol Deviations (N=63)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged alive</td>
<td>145 (71%)</td>
<td>95 (73%)</td>
<td>1.25 (0.67, 2.34)</td>
<td>0.49</td>
<td>1.73 (0.80, 3.74)</td>
<td>0.16</td>
</tr>
<tr>
<td>CPC 1 or 2</td>
<td>125 (62%)</td>
<td>86 (66%)</td>
<td>1.70 (0.85, 3.06)</td>
<td>0.07</td>
<td>2.77 (1.31, 5.85)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>STEMI Population Outcomes</th>
<th>MRC Protocol (N=112)</th>
<th>Protocol Deviations (N=23)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged alive</td>
<td>82 (73%)</td>
<td>75 (74%)</td>
<td>1.65 (0.65, 4.06)</td>
<td>0.45</td>
<td>1.89 (0.48, 7.48)</td>
<td>0.36</td>
</tr>
<tr>
<td>CPC 1 or 2</td>
<td>72 (64%)</td>
<td>65 (64%)</td>
<td>1.63 (0.83, 3.26)</td>
<td>0.09</td>
<td>1.10 (0.53, 2.32)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

### Table 6. Outcomes Based on the Presence or Absence of Revascularization Regardless of Timing to CCL Access

<table>
<thead>
<tr>
<th>Overall Population</th>
<th>PC1 or GAMI (N=139)</th>
<th>No PC1 or GAMI (N=176)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged alive</td>
<td>227 (72%)</td>
<td>112 (72%)</td>
<td>1.81 (1.13, 3.14)</td>
<td>0.01</td>
<td>2.55 (1.32, 4.92)</td>
<td>0.005</td>
</tr>
<tr>
<td>CPC 1 or 2</td>
<td>197 (63%)</td>
<td>102 (72%)</td>
<td>2.09 (1.31, 3.30)</td>
<td>0.002</td>
<td>3.04 (1.36, 5.69)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

GAMI indicates coronary artery lesion graft; CCL, cardiac catheterization lab; OR, odds ratio; PC1, percutaneous coronary intervention.

*Adjusted for age, sex, race, history of PCI, GAMI, myocardial infarction, diabetes mellitus, hypertension, congestive heart failure, hyperlipidemia, tobacco use, prior location of arrest, bystander cardiopulmonary resuscitation witnessed arrest.

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**Immediate Percutaneous Coronary Intervention Is Associated With Better Survival After Out-of-Hospital Cardiac Arrest**

**Insights From the PROCAT (Parisian Region Out of Hospital Cardiac Arrest) Registry**

Florence Dumas, MD; Alain Cariou, MD; Stéphane Manzo-Silberman, MD; David Grimaldi, MD; Benedikt Vivien, MD; Julien Rosencher, MD; Jean-Philippe Empapa, MD; Pierre Carli, MD; Jean-Paul Mira, MD; Xavier Joeven, MD; Christian Spaubling, MD

**Background**—Acute coronary occlusion is the leading cause of cardiac arrest. Because of limited data, the indications and timing of coronary angiography and angioplasty in patients with out-of-hospital cardiac arrest are controversial. Using data from the Parisian Region Out of Hospital Cardiac Arrest prospective registry, we performed an analysis to assess the effect of an invasive strategy on hospital survival.

**Methods and Results**—Between January 2003 and December 2008, 714 patients with out-of-hospital cardiac arrest were referred to a tertiary center in Paris, France. In 435 patients with no obvious extracardiac cause of arrest, an immediate coronary angiogram was performed at admission followed, if indicated, by coronary angioplasty. At least 1 significant coronary artery lesion was found in 304 (70%) patients, in 120 (90%) of 134 patients with ST-segment elevation on the ECG performed after the return of spontaneous circulation, and in 124 (88%) of 141 patients without ST-segment elevation. The hospital survival rate was 40%. Multivariable analysis showed successful coronary angioplasty to be an independent predictive factor of survival, regardless of the postresuscitation ECG pattern (odds ratio, 2.06; 95% CI, 1.16 to 3.66).

**Conclusions**—Successful immediate coronary angioplasty is associated with improved hospital survival in patients with or without ST-segment elevation. Therefore, our findings support the use of immediate coronary angiography in patients with out-of-hospital cardiac arrest with no obvious noncardiac cause of arrest regardless of the ECG pattern. (Circ Cardiovasc Interv. 2010;3:200-207.)

**Key Words:** cardiac arrest • PCI • angioplasty • catheterization • electrocardiography
PCI was associated with increased survival irrespectively of ECG

Multivariate analysis
PCI associated with better prognosis

Figure 3. Multivariate logistic regression analysis of early predictors of survival in patients with OHCA without obvious extracardiac causes. PSA indicates pulseless electrical activity.
ROC PRIMED data showing that although only 19.2% of patients gained access to the CCL early they had significant survival advantage. C.W. Callaway et al. Resuscitation 85 (2014) 657–663


Camuglia et al meta-analysis without the two largest and newest cohorts

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Acute angiography</th>
<th>No acute angiography</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurore 2011</td>
<td>38 133</td>
<td>36 312</td>
<td>8.2%</td>
<td>2.86 [1.86, 4.46]</td>
</tr>
<tr>
<td>Bres-jeppesen 2012</td>
<td>129 198</td>
<td>87 162</td>
<td>9.3%</td>
<td>1.61 [1.05, 2.47]</td>
</tr>
<tr>
<td>Brown 1999</td>
<td>4 10</td>
<td>16 27</td>
<td>2.0%</td>
<td>1.13 [0.26, 5.01]</td>
</tr>
<tr>
<td>Crozier 2011</td>
<td>54 91</td>
<td>6 20</td>
<td>4.7%</td>
<td>3.41 [1.20, 9.67]</td>
</tr>
<tr>
<td>Gruener 2011</td>
<td>80 154</td>
<td>57 430</td>
<td>9.3%</td>
<td>7.07 [4.64, 10.76]</td>
</tr>
<tr>
<td>Hollenbeck 2013</td>
<td>80 122</td>
<td>71 147</td>
<td>8.7%</td>
<td>2.84 [1.24, 3.34]</td>
</tr>
<tr>
<td>Mooney 2011</td>
<td>63 101</td>
<td>15 39</td>
<td>6.5%</td>
<td>2.65 [1.24, 5.67]</td>
</tr>
<tr>
<td>Nonissova 2012</td>
<td>18 35</td>
<td>12 35</td>
<td>5.2%</td>
<td>2.83 [0.78, 5.31]</td>
</tr>
<tr>
<td>Nielsen 2009</td>
<td>303 429</td>
<td>187 507</td>
<td>10.6%</td>
<td>2.95 [2.78, 3.13]</td>
</tr>
<tr>
<td>Reynolds 2009</td>
<td>40 63</td>
<td>22 33</td>
<td>5.0%</td>
<td>0.87 [0.36, 2.11]</td>
</tr>
<tr>
<td>Sterte 2012</td>
<td>44 61</td>
<td>88 179</td>
<td>7.5%</td>
<td>2.68 [1.42, 5.13]</td>
</tr>
<tr>
<td>Torne 2011</td>
<td>76 145</td>
<td>9 29</td>
<td>5.9%</td>
<td>2.45 [1.04, 5.74]</td>
</tr>
<tr>
<td>Woldo 2013</td>
<td>57 84</td>
<td>7 26</td>
<td>5.1%</td>
<td>5.73 [2.13, 15.27]</td>
</tr>
<tr>
<td>Werling 2007</td>
<td>19 28</td>
<td>16 57</td>
<td>4.7%</td>
<td>9.02 [1.48, 5.82]</td>
</tr>
<tr>
<td>Zasutin 2012</td>
<td>33 48</td>
<td>21 45</td>
<td>5.0%</td>
<td>2.51 [1.08, 5.69]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1752 2048</td>
<td>100.0%</td>
<td>2.77 [2.06, 3.72]</td>
<td></td>
</tr>
</tbody>
</table>

THE ACCESS TRIAL

- NIH Phase III multicenter clinical trial for NSTEMI patients after resuscitated VF.
- Yannopoulos/ Aufderheide co-PIs
- Definitive trial in 880 patients
- Primary outcome survival to Hospital Discharge with good neurological function.
- Results in 4 years
Clinical Equipoise

- Observational case series results are encouraging, but subject to selection bias and unmeasured confounders
- As a result, wide variation in clinical practice exists with **two standards of care** practiced in the United States:
  - Initial cardiac catheterization laboratory (CCL) admission
  - Initial ICU admission
- Clinical and physiologic validity to intervene in any individual case with one of these two treatment options is unknown
- Professional guideline organizations recommend a randomized trial
- Given our current understanding, clinical equipoise exists for the ACCESS Trial
Purpose/Specific Aim

• Determine survival to hospital discharge with Modified Rankin Scale Score (MRS) ≤ 3 in adult patients (18-75 years old) resuscitated from VF/VT OHCA with no-STE on emergency department ECG randomized to receive either:
  1) Initial CCL admission, or
  2) Initial ICU admission

Significance

• An estimated 120-130,000 patients have cardiac arrest due to VF/VT every year.
• Of those 40-50% survive to hospital admission (=50,000-65,000 patients),
• With an estimate of an absolute 15% increase in functionally favorable survival rate, an additional 9000 to ~12000 patients could be saved each year in the United States alone.
Inclusion Criteria

• Adults presumed or known to be 18-75 years old
• Resuscitated from OOHCA
• Initial cardiac arrest rhythm of pulseless VF/VT
  – including patients shocked with an AED
• No ST-segment elevation MI on ED 12-lead ECG
  – interpreted by a physician

Exclusion Criteria

• Initial non-shockable OOHCA rhythm (PEA or asystole),
• Valid do not resuscitate orders (DNR),
• Blunt, penetrating, or burn-related injury, drowning, electrocution or known overdose,
• Known prisoners,
• Known pregnancy,
• STEMI on ED 12-lead ECG,
• Absolute contraindications to emergent coronary angiography including,
  – Known anaphylactic reaction to angiographic contrast media,
  – Active gastrointestinal or internal bleeding, or
  – Severe concomitant illness that drastically shortens life expectancy or increases risk of the procedure.
• Suspected or confirmed intracranial bleeding
• Refractory cardiac arrest (prior to randomization)
• Patients meeting ACCESS Trial eligibility criteria initially seen in an outside hospital and then transferred to an ACCESS Trial participating hospital
• Unavailability of the cardiac catheterization laboratory
Outcome Measures

• Primary Study Endpoint
  – Survival to hospital discharge with MRS ≤ 3

• Secondary Study Endpoints
  – Survival with MRS ≤ 3 at 3 months
  – In-hospital
    • Survival to hospital discharge, mRS score, CPC score, mean peak troponin level, mean ejection fraction, mean length of ICU stay, mean hospitalization duration in patients who survive to hospital discharge, and the incidence of and mean length of rehabilitation
  – 3-months
    • Survival to 3 months, survival to 3 months with mRS ≤ 3, functional status at 3 months (mRS score, CPC score, Adult Lifestyle and Function Interview [ALFI] version of the Mini-Mental Status Exam [MMSE], Health Utilities Index Mark 3 [HUI3], and Geriatric Depression Scale [T-GDS]), incidence and length of rehabilitation, incidence of congestive heart failure, incidence of re-hospitalization over 3 months, and incidence and time to return to work.

12-lead ECG STEMI Criteria

• The 12-lead ECG MUST be the emergency department 12-lead ECG!

• Out-of-hospital 12-lead ECG NOT acceptable for determining patient eligibility! Out-of-hospital 12-leads:
  • Can be electrically altered in the immediate post-defibrillation period
  • May undergo electrical evolution with time
  • Generally are of poorer quality than ED 12-lead ECGs and can have significant artifact
Study Algorithm

- Patient arrives in ED
- Verify VF criteria
- Research personnel attempt to contact Legally Authorized Representative (LAR) first 45 minutes following ED arrival
- Randomized within 45 minutes by:
  - Written informed consent, or
  - Exception from informed consent (EFIC)

- Initial CCL Admission
  - No specified research treatment
  - Hospital Discharge
    - Survival with mRS ≤ 3
  - 3 months
    - Survival with mRS ≤ 3
    - Functional/cognitive assessment

- Initial ICU Admission
  - No specified research treatment
  - Hospital Discharge
    - Survival with mRS ≤ 3
  - 3 months
    - Survival with mRS ≤ 3
    - Functional/cognitive assessment

Refractory OHCA due to VF

- If resuscitated VF patients have high prevalence of CAD and acute coronary events then refractory VF patients should have more substantial disease.
- If so, one way to save the other 60% of VF patients that are pronounced dead in the field or the ED is to bring them to the CCL with ongoing CPR and resuscitate them in the CCL.
Extracorporeal Cardiopulmonary Resuscitation (ECPR)

**stub resuscitation 2014**

**CHEER Study Patients**

Refactory cardiac arrest ($>$30mins)

- Initial Rhythm
  - VF ($n=11$)
- ROSC in E & TC prior to ECMOsupport ($n=2$)
- ECPR ($n=9$)
- ROSC ($n=9$)
- No ROSC ($n=13$)
- Die prior to ECMO wean ($n=6$)
- ECMO wean ($n=6$)
- Die post ECMO wean ($n=6$)
- Survive ($n=11$)

- In-hospital cardiac arrest ($n=17$)
  - Initial Rhythm
    - VF ($n=4$)
    - Asystole ($n=3$)
    - PEA ($n=10$)
- ECPR ($n=15$)
- ROSC ($n=6$)
- No ROSC ($n=11$)
- Die prior to ECMO wean ($n=6$)
- ECMO wean ($n=6$)
- Die post ECMO wean ($n=6$)
- Survive ($n=11$)

**Fig. 1.** Outcomes of 26 patient with refactory cardiac arrest. CHEER - Mechanical CPR, Hypothermia, ECMO and Early Reperfusion. ECMO - Extracorporeal Membrane Oxygenation, E & TC - Emergency and Trauma Center, VF - Ventricular Fibrillation, ROSC - return of spontaneous circulation, ECMO - extracorporeal membrane oxygenation, ECPR - extracorporeal membrane oxygenation/reperfusion.
2015 AHA ECC Treatment Recommendation

http://ECCGuidelines.heart.org

- There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest.
- In settings where it can be rapidly implemented, ECPR may be considered for select patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support. (Class IIb, LOE C-LD)

Role of Epinephrine and Extracorporeal Membrane Oxygenation in the Management of Ischemic Refractory Ventricular Fibrillation
A Randomized Trial in Pigs

Jason A. Bartos, MD, PhD, Sebastian Vociu, MD, Timothy R. Matsuzaka, BA, Adamantios Tsangaris, MD, Georgios Sidiras, MD, PhD, Brett A. Gootschi, MD, Stephen A. George, MD, PhD, Matthew Olson, MD, Kailambahi Chandrashekhar, MS, Jennifer N. Rees, PhD, Kathleen Carlson, MD, Pierre Sebastian, BEME, Scott McKeilie, BS, Ganesh Ravendran, MD, Tom P. Aufderheide, MD, Demetris Yannopoulos, MD

- A porcine model of refractory VF cardiac arrest was developed, including initiation of VF using endovascular occlusion of the proximal LAD followed by 5 min of untreated VF. Resuscitation begins with 10 min of high-quality CPR followed by 35 min of ACLS and reconstitution of coronary flow.
- A 2 × 2 study design was used with animals randomized to use of epinephrine or placebo during ACLS and then again randomized to ECMO or no ECMO at the time of reinitiation of coronary flow.
- ECMO-facilitated coronary reperfusion and hemodynamic stabilization improved 4-h survival compared with CPR-facilitated reperfusion and standard ACLS in a porcine model of refractory VF cardiac arrest.
The importance of perfusion and the inefficiency of standard ACLS for prolonged CPR.

**Experimental paper**

Sodium nitroprusside enhanced cardiopulmonary resuscitation improves short term survival in a porcine model of ischemic refractory ventricular fibrillation.

Demetris Yannopoulos, Jason A. Bartos, Stephen A. George, George Sideris, Sebastian Voicu, Brett Oestreich, Timothy Matsuura, Kadambari Shekar, Jennifer Rees, Tom P. Aufderheide

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**ARTICLE INFO**

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Received in revised form 16 September 2016
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Sodium nitroprusside enhanced CPR
Ventricular Fibrillation

**ABSTRACT**

Introduction: Sodium nitroprusside (SNP) enhanced CPR (SNP/CPR) demonstrates increased vital organ blood flow and survival in multiple porcine models. We developed a new, coronary occlusion/ischemia model of prolonged resuscitation, mimicking the majority of out-of-hospital cardiac arrests presenting with shockable rhythms.

Hypothesis: SNP/CPR will increase short term (4-h) survival compared to standard 2015 Advanced Cardiac Life Support (ACLS) guidelines in an ischemic-refractory ventricular fibrillation (VF) prolonged CPR model.

Methods: Sixteen anesthetized pigs had the aortal left anterior descending artery occluded leading to ischemic VF arrest. VF was untreated for 5 min. Basic life support was performed for 3 min. An anesthetist SD (EMS animal), animals received either SNP/CPR (n=8) or standard ACLS (n=8). Defibrillation (200J)
Model

D. Yannopoulos et al. / Resuscitation 110 (2017) 6–11

Animal images

Patient’s image

Temporal built up of lactic acid

D. Yannopoulos et al. / Resuscitation 110 (2017) 6–11

SNPeCPR
Control

Lactic acid blood levels (mmol/L)

Minutes from initiation of CPR.

p= 0.0012
Blood flow and avoidance of ischemic injury improves survival

Fig. 4. Kaplan–Meier 4-h survival curves. Survival curves for animals treated with standard and SNPeCPR ACLS are shown. Animals that were treated with SNPeCPR ACLS had a significant increase in 4-h survival.

The contribution of VF in over all survival.

2011-2016 Minnesota OHCA ages 18-75

Survival to DC with GOOD CPC
- Shockable Rhythm
- Unshockable Rhythm

84%
773/923

16%
MHIF CV Grand Rounds – October 9, 2017

**2411 OHCA VF patients**

- 773 (or 32% 773/2411) Survived to Hospital DC with CPC 1&2
- Another 528 died after hospital admission
- 54% (1301) Had ROSC
- 46% (1110) Never had ROSC. Declared dead in the Field

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**ORIGINAL RESEARCH**

**Minnesota Resuscitation Consortium’s Advanced Perfusion and Reperfusion Cardiac Life Support Strategy for Out-of-Hospital Refractory Ventricular Fibrillation**

Demetris Yannopoulos, MD; Jason A. Barros, MD, PhD; Cindy Martin, MD; Ganesh Ravendran, MD, MPH; Emil Misinou, MD, PhD; Marc Cerrato, MD; R. L. Frascorni, MD; Alexander Tremblay, BS; Kevin Sipirell, MD; Ranjit John, MD, PhD; Stephen George, MD, PhD; Kathleen Carlson, MD; Melissa E. Brunsvold, MD; Santiago Garcia, MD; Tom F. Autenried, MD

**Background**—In 2015, the Minnesota Resuscitation Consortium (MRC) implemented an advanced perfusion and reperfusion life support strategy designed to improve outcome for patients with out-of-hospital refractory ventricular fibrillation/ventricular tachycardia (VF/VT). We report the outcomes of the initial 3-month period of operations.

**Methods and Results**—Three emergency medical services systems serving the Minneapolis–St. Paul metro area participated in the protocol. Inclusion criteria included age 18 to 75 years, body habitus accommodating automated Lund University Cardiac Arrest System (LUCAS) cardiopulmonary resuscitation (CPR), and estimated transfer time from the scene to the cardiac catheterization laboratory of ≤50 minutes. Exclusion criteria included known terminal illness, Do Not Resuscitate/Do Not Intubate status, traumatic arrest, and significant bleeding. Refractory VF/VT arrest was defined as failure to achieve sustained return of spontaneous circulation after treatment with 3 direct current shocks and administration of 300 mg of intravenous/intracoronary amiodarone. Patients were transported to the University of Minnesota, where emergent advanced perfusion strategies (intracoronary membrane reperfusion; ECMO), followed by coronary angiography and primary coronary intervention (PCI), were performed, when appropriate. Over the first 3 months of the protocol, 27 patients were transported with ongoing mechanical CPR. Of these, 18 patients met the inclusion and exclusion criteria. ECMO was placed in 83%. Seventy-eight percent of patients had significant coronary artery disease with a high degree of complexity and 67% received PCI. Seventy-eight percent of patients survived to hospital admission and 56% (10 of 18) survived to hospital discharge, with 52% (9 of 18) achieving good neurological function (cerebral performance categories 1 and 2). No significant ECMO-related complications were encountered.

**Conclusions**—The MRC advanced perfusion VF/VT protocol is feasible and led to a high functionally favorable survival rate with few complications. (J Am Heart Assoc. 2016;5:e003732 doi: 10.1161/JAHA.116.003732)
Coronary Artery Disease in Patients With Out-of-Hospital Refractory Ventricular Fibrillation Cardiac Arrest

JACC 2017;70:1109–17

ABSTRACT

BACKGROUND: The prevalence of coronary artery disease (CAD) among patients with refractory out-of-hospital (OH) ventricular fibrillation (VF)/ventricular tachycardia (VT) cardiac arrest is unknown.

OBJECTIVES: The goal of this study was to describe the prevalence and complexity of CAD and report survival to hospital discharge in patients experiencing refractory VF/VT cardiac arrest treated with a novel protocol of early transport to a cardiac catheterization laboratory (CCL) for extracorporeal life support (ECLS) and revascularization.

METHODS: Between December 1, 2015, and December 1, 2016, consecutive adult patients with refractory OH VF/VT cardiac arrest requiring ongoing cardiopulmonary resuscitation were transported by emergency medical services to the CCL. ECLS, coronary angiography, and percutaneous coronary intervention were performed, as appropriate. Functionally favorable survival to hospital discharge (Cardiac Performance Category 1 or 2) was determined. Outcomes in a historical comparison group were also evaluated.

RESULTS: Sixty-two (86%) of 72 transported patients met emergency medical services transport criteria. Fifty-five (89%) of the 62 patients met criteria for continuing resuscitation on OH arrival, 59 had return of spontaneous circulation, 50 received ECLS, and all 55 received coronary angiography. Forty-six (84%) of 55 patients had significant CAD. 36 (64%) of 56 had acute thrombotic lesions, and 46 (84%) of 55 had percutaneous coronary intervention with 2.7±2.0 stents deployed per patient. The mean ST/EFFAX score was 29±13.9. Twenty-six (43%) of 62 patients were discharged alive with Cardiac Performance Category 1 or 2 versus 26 (35.3%) of 72 in the historical comparison group (odds ratio: 4.0, 95% confidence interval: 1.87 to 7.3, p < 0.00001).

CONCLUSIONS: Complex but treatable CAD was prevalent in patients with refractory OH VF/VT cardiac arrest who also met criteria for continuing resuscitation in the CCL. A systems approach using ECLS and reperfusion seemed to improve functionally favorable survival. (J Am Coll Cardiol. 2017;70:1109-17) © 2017 by the American College of Cardiology Foundation.

Central Illustration: Refractory Cardiac Arrest Due to VF/VT and the University of Minnesota ECLS/PCI Protocol

Protocol inclusion criteria

- Determine Early EMS Transport Criteria
  - OHCA of presumed cardiac etiology
  - VF or VT as first presenting rhythm
  - 18-75 years of age
  - Received three EMS-delivered DC shocks and 300mg of amiodarone IV/IO without achieving ROSC
  - Body morphology able to accommodate LUCAS™ automated CPR device
  - Estimated transfer time from the scene to the CCL of < 30 minutes.
- If Patient Meets Early EMS Transport Criteria, Transport to CCL
  - Ongoing Mechanical CPR with ITD
  - Continued ACLS (limit epinephrine to 3 mg total), Defibrillation PRN en Route

Patient (age 18-75) with on-going CPR with refractory VF/VT that met the criteria entered the CCL (All patients with LUCAS+ITD)

Enter the CCL with CPR on going or with ROSC for initial assessment

Arterial and venous access under ultrasound, Obtain ABGs and serum lactate Determine the presence of the CCL Resuscitation Discontinuation Criteria:
- ETCO2 on CCL Arrival < 10 mm Hg
- PaO2 < 50 mm Hg or O2 Sat < 85%
- Serum Lactate > 18 mmol/L

Patient has one or more of the above criteria. Terminate Resuscitation Declare Dead

NONE PRESENT:
- Place AV ECMO
- Angiography
- PCI WHEN NECESSARY

Continue ECLS/ACLS for up to 90min

If return of spontaneous cardiac function is achieved then admit to CICU
If not, pronounce death.
72 Patients that presented with VF were transported by EMS after 3 unsuccessful DC shocks and amiodarone administration.

55 patients received full CCL treatment:
- 5 patients had ROSC before arrival
- 50 patients were placed on ECLS

47 patients were admitted to the ICU.

8 were declared dead after ECLS was initiated due to inability to reestablish organized rhythm after 90 minutes.

10 Excluded Not Meeting Early Transport Inclusion Criteria (Protocol Violations)
- 3 - Manual CPR Only
- 1 - Pectus Excavatum
- 2 - Morbid Obesity
- 1 - Time from 911 to CCL > 90 minutes
- 1 - Age = 80 years; terminal cancer
- 1 - Stage IV renal cell Ca (59 yo man)
- 2 - DNR discovered on arrival

7 were declared dead because of failure to meet the ECLS initiation criteria:
- 1 - ETCO2 on arrival < 10mm Hg
- 3 - PaO2 < 50 mmHg or O2 Sat < 85%
- 3 - Lactate > 18

62 Patients Transported Met Early Transport Protocol Criteria

Patient and Arrest Characteristics

Patient Characteristics of refractory VF/VT patients (N=62) N (%)  
- Sex  
  - Male 44 (71)
  - Female 18 (29)
- Age (yrs)
  - <40 5 (8)
  - 40-60 33 (53)
  - >60-75 24 (39)
- Ethnicity
  - White 49 (80)
  - Black 9 (14)
  - Other 4 (6)
- Known Comorbidities
  - Diabetes 12 (19)
  - CAD 5 (9)
  - HTN 30 (48)
  - Smoking 14 (22.5)
  - Alcoholism 3 (5)
  - Hyperlipidemia 23 (36)
  - CABG 5 (9)
  - Congestive heart disease 8 (13)

Cardiac Arrest Characteristics and EMS/CCL times (N=62) N (%)  
- Arrest location
  - Home 34 (55)
  - Public place 28 (45)
- Initial Cardiac Rhythm
  - VF/VT 62 (100)
  - Other 0
- Bystander CPR
  - Yes 52 (84)
  - No 10 (16)
- Times (min)
  - 911 to first responder 6.2±4.6
  - 911 to CCL arrival 58±17
  - 911 to ECLS 64.0±13.2
  - CCL arrival - on ECMO 6.1±1.8
  - CCL arrival - balloon time 12.0±3.0

Yannopoulos, et al, JACC, 2017
Survivors vs. Deaths

<table>
<thead>
<tr>
<th>Refractory VF/VT patients</th>
<th>Survivors (28)</th>
<th>Deaths (34)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57 ± 11</td>
<td>59 ± 10</td>
<td>0.3</td>
</tr>
<tr>
<td>Bystander CPR</td>
<td>96%</td>
<td>71%</td>
<td>0.1</td>
</tr>
<tr>
<td>911 call to first response arrival (min)</td>
<td>4.1 ± 4.6</td>
<td>7.1 ± 4.6</td>
<td>0.03</td>
</tr>
<tr>
<td>911 call to CCL entry (min)</td>
<td>55 ± 16.7</td>
<td>62 ± 14.9</td>
<td>0.07</td>
</tr>
<tr>
<td>CCL entry - on ECLS (min)</td>
<td>6.2 ± 2</td>
<td>5.8 ± 3</td>
<td>0.5</td>
</tr>
<tr>
<td>pH on ECLS opening ABG</td>
<td>7.13 ± 0.1</td>
<td>7.04 ± 0.2</td>
<td>0.08</td>
</tr>
<tr>
<td>ETCO2 on arrival</td>
<td>42 ± 15</td>
<td>31 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>Lactate at CCL arrival</td>
<td>10.1 ± 3.9</td>
<td>13.3 ± 3.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Presence of CAD</td>
<td>88%</td>
<td>68%</td>
<td>0.01</td>
</tr>
<tr>
<td>Witnessed arrest</td>
<td>88%</td>
<td>90%</td>
<td>0.5</td>
</tr>
<tr>
<td>Intermittent ROSC before ECLS</td>
<td>67%</td>
<td>19%</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Yannopoulos, et al, JACC, 2017

Coronary Artery Disease

Significant Coronary Disease (≥ 70%)
- No 16%
- Yes 84%

Extent of Coronary Artery Disease
- Three Vessel 44%
- Single Vessel 30%
- Two Vessel 26%

Lesion Complexity
- Prior Coronary Artery Bypass Grafts: 5 (9%)
- Chronic Total Occlusion Present: 18 (33%)
- Patients with Acute Thrombotic Lesions: 35 (64%)
- SYNTAX Score: 29.4 ± 13.9

Yannopoulos, et al, JACC, 2017
Treatments Provided

<table>
<thead>
<tr>
<th>Treatments Provided (N=55)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracorporeal membrane oxygenation</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (91%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (45%)</td>
</tr>
<tr>
<td>No</td>
<td>30 (55%)</td>
</tr>
<tr>
<td>Coronary stenting</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (82%)</td>
</tr>
<tr>
<td>No</td>
<td>10 (18%)</td>
</tr>
<tr>
<td>Average number of stents per patient</td>
<td>2.7 ± 2.0</td>
</tr>
<tr>
<td>Intravascular hypothermia initiated</td>
<td>55 (100%)</td>
</tr>
</tbody>
</table>

Yannopoulos, et al, JACC, 2017

Historical Comparison

Yannopoulos, et al, JACC, 2017
Conclusions

• Complex but treatable CAD was prevalent in patients with refractory OH VF/VT cardiac arrest.

• A systems approach using ECLS and reperfusion seemed to improve functionally favorable survival.

• A randomized trial is needed and The ARREST trial will be starting Summer 2018.
ROSC AFTER 120 minutes of CPR

61 y.o. man with prolonged CPR with poor oxygenation
53 yo woman with EtOH
### Complications

<table>
<thead>
<tr>
<th>CT Chest</th>
<th>Overall (52)</th>
<th>Survivors (28)</th>
<th>Deaths (18)</th>
<th>Brain Death (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rib Fractures</td>
<td>19/52 (37%)</td>
<td>7/28 (25%)</td>
<td>8/18 (44%)</td>
<td>4/6 (67%)</td>
</tr>
<tr>
<td>Lung Injury</td>
<td>39/52 (75%)</td>
<td>19/28 (68%)</td>
<td>15/18 (83%)</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>4/52 (7.7%)</td>
<td>3/28 (11%)</td>
<td>0%</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>Pneumothorax Requiring Chest tube</td>
<td>2/52 (3.8%)</td>
<td>2/28 (7.1%)</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thoracic Bleed</td>
<td>5/52 (9.6%)</td>
<td>1/28 (3.6%)</td>
<td>3/18 (17%)</td>
<td>1/6 (17%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CT Abd/Pelvis</th>
<th>Overall (52)</th>
<th>Survivors (28)</th>
<th>Deaths (18)</th>
<th>Brain Death (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Bleed</td>
<td>4/52 (7.7%)</td>
<td>2/28 (7.1%)</td>
<td>2/18 (11%)</td>
<td>0%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>4/52 (7.7%)</td>
<td>2/28 (7.1%)</td>
<td>2/18 (11%)</td>
<td>0%</td>
</tr>
<tr>
<td>RP Bleed</td>
<td>4/52 (7.7%)</td>
<td>2/28 (7.1%)</td>
<td>2/18 (11%)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Bartos, et al, under review

### Impaired Glucose Regulation

**Glucose**

- Survivors
- Deaths
- Brain Death

**Insulin Requirement**

- Survivors
- Deaths
- Brain Death

Bartos, et al, under review
Creighton Clemens

Creighton Clemens, an independent business owner, had not experienced any recent health concerns when he went to bed as usual on the night of March 20, 2016. But the night would be anything but usual.

Wendy, who Creighton calls his “sweetie”, woke up to strange noises and realized that it was Creighton. She quickly called 911. Wendy had some basic knowledge of CPR and with coaching from dispatch she started and continued CPR until Crystal Police and paramedics arrived. The paramedics recognized that Creighton could be a candidate for the new sudden cardiac arrest protocol and notified Dr. Vamopoulos. Creighton was transported to the University of Minnesota, where he was taken to the cath lab and had alerts placed.

Creighton is back to working and living life, maybe a little smarter and trying to live a healthier lifestyle.

Turning Miracles into Everyday Events!

The MN Resuscitation Consortium works with partners across Minnesota to improve outcomes from Sudden Cardiac Arrest. By focusing on the key systems that affect outcomes - bystander training, first responders, EMS and hospital response - change can occur and the number of Minnesota’s survival rate is set compared to national survival of 7%. This has been accomplished by increased bystander training and awareness, new protocols for BLS and ALS responders with high performance CPR and advanced technologies, and initiatives to rapidly move resuscitated SCA patients to the cath lab for faster treatment, www.mcn.umn.edu.

Dennis Suppert

Dennis is single and a retired veteran from St. Joseph’s hospital. He likes to play cards and bingo. He is involved in church and likes to walk or take the bus to downtown.

On the December 3rd, the date of his cardiac event, he was feeling good. He went to Shakey’s restaurant in St. Paul and some patrons stated that he had stood up and fell collapsed. An employee conducted CPR until St. Paul Fire arrived. EMS contacted Dr. Vamopoulos to activate the new protocol. Dennis was brought to the University of Minnesota. After he was placed on mechanical support to take over his heart and lung function (ECMO). His blockage in his coronary artery that was responsible for his cardiac arrest was treated successfully. His heart and vital organs were supported for a few days and he was cooled to protect his brain from injury. A few days later Dennis was discharged with a good heart and normal brain function. His family knew the chances were low that Dennis would make it through. What the doctors did was a miracle. They were thankful to EMS and the cutting edge procedures that the doctors performed. Without that, Dennis would not have survived and be with them today.

Dennis is fully back to his normal daily activities and enjoying life.

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26 year old patient.

WPW induced VF on 4th of July 2017 in the pool. 70-minutes of CPR before ECPR initiation: 20mmol/L lactic acid Above cut point!!!

One month later back to UoM dental school.

Four important studies suggest improved neurologically intact survival if ECPR performed during cardiac arrest

• “CHEER Trial” in Australia– series of 11 ECPR patients with OHCA,  
  – 45% neuro-intact survival
• Morimura et al in Japan– series of 139 ECPR cases  
  – 51% neuro-intact survival
• “Save-J Study” in Japan– series of 454 ECPR cases  
  – 12% neurologically favorable survival
• Minnesota Resuscitation Consortium 22 months – 108 ECPR patients 45% neurologically favorable survival

**BEST OUTCOMES if ECPR initiated within 60 minutes of arrest!**
Redefining ACS continuum

Thrombus Formation and ACS

Old Terminology:
- UA
- NQMI
- STEMI

New Terminology:
- Non-ST-Segment Elevation Acute Coronary Syndrome (ACS)
- ST-Segment Elevation Acute Coronary Syndrome

In-hospital mortality rate:
- 2%
- 5%
- <10%
- 50%

Door to needle: 2-3 minutes
Needle to on-ECMO time average 4 min for a door to ECMO 6.5 min

There is light in the future of Resuscitation Science!