ECMO-Facilitated Resuscitation:
Insights and a New Understanding of the Process of Death

Tom P. Aufderheide MD, MS, FACEP, Hon FACC, FAHA
Professor of Emergency Medicine
Director, Resuscitation Research Center
Department of Emergency Medicine
Medical College of Wisconsin

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Presenter Disclosure Information

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  - The contents of this presentation are solely the responsibility of the authors and do not necessarily represent the official views of the NIH, NHLBI, or NINDS.
- **Unlabeled/Unapproved Uses Disclosure:** Have performed studies with ResQPOD®, ResQPUMP™ in patients with cardiac arrest
  - No financial interest whatsoever in Advanced Circulatory Systems, Inc., ResQPOD®, ResQPUMP®. any device or company
- **Company Sponsored Research**
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- **Patent**
  - **No:** US 10,828,436 B2: Use of the Nobel Gas, Argon, in Cardiac Arrest
- **Volunteer**: Vice President: Take Heart America, Immediate Past President, Citizen CPR Foundation, National American Heart Association, 3CPR Leadership Committee, Member, National Academy of Medicine (NAM); Institute of Medicine (IOM) Report on Cardiac Arrest, Chaired NAM Workshop, Executive Committee National Cardiac Arrest Collaborative (NCAC)

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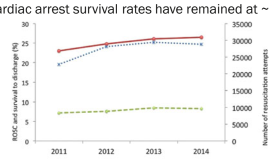
State of Cardiac Arrest Survival

- 400,000 OHCAs/year in the US
- Overall, 7% survival rate
- 372,000 deaths/year
- 3rd leading cause of death in the United States
- National cardiac arrest survival rates have remained at ~ 7% for decades



Emerg Med J. 2016 Jul; 33(7): 448–451.

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Objectives

- ECMO-Facilitated Resuscitation of Refractory Out-of-Hospital VF
  - First observational case series
  - Discovery of the cause of refractory VF cardiac arrest
  - First randomized clinical trial (The ARREST Trial)
  - Insights
- New Understanding of the Process of Death
- Vision for the future

Demetris Yannopoulos, MD
Professor of Medicine, Division of Cardiology
The Robert Eddy Endowed Chair in Cardiovascular Resuscitation
Medical Director, Center for Resuscitation Medicine
University of Minnesota

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History

- In 2015, the Minnesota Resuscitation Consortium (MRC) published its first 3-month experience
  - Years of development with strong, multidisciplinary, community-wide collaboration with input from interventional cardiology, emergency medicine, and out-of-hospital EMS providers
- Components
  - Early EMS mobilization for VF (3 failed shocks ± amiodarone)
  - Simplified ECMO team mobilization with 1 call from EMS dispatch
  - Small core group of ECMO cannulators (e.g., high volume, consistency, minimize complications)
  - Dedicated ICU team with strong, cross-specialty support and <u>**no physician-recommended WLST**</u>
- Entry criteria
  - Aged 18-75
  - Primary, out-of-hospital VF/VT cardiac arrest only with 3 failed shocks ± amiodarone
  - Body habitus fits LUCAS CPR ± ITD
  - Estimated transfer time < 30 minutes
- Exclusion criteria
  - Nursing home residents; DNR; terminal illness; traumatic cardiac arrest; primary PEA/asystole; bleeding

ECMO
MN Mobile Resuscitation Consortium

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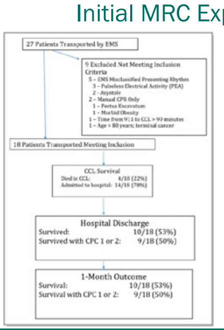
Initial MRC Experience*



Conclusions

1. ECMO program was feasible
2. High functionally favorable survival rates (50%)
3. No significant ECMO related complications

*J Am Heart Assoc. 2016;5:e003732

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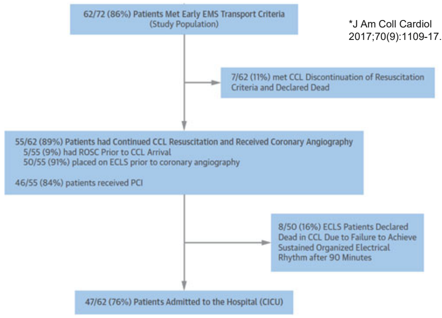
CAD in Patients with Refractory VF OHCA*



*J Am Coll Cardiol 2017;70(9):1109-17.

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84% Incidence of Coronary Artery Disease

TABLE 2 Angiographic Findings and Procedural Outcomes

Angiographic findings	
Normal or clinically insignificant CAD (≤70% stenosis)	9/55 (16)
Clinically significant CAD (>70% stenosis)	46/55 (84)
Single-vessel disease	14/46 (30)
2-Vessel disease	12/46 (26)
3-Vessel disease	20/46 (44)
Disease location	
Left main	7/46 (15)
LAD	40/46 (87)
LCx	24/46 (52)
RCA	23/46 (50)
Prior coronary artery bypass graft	5/55 (9)
Chronic total occlusion present	18/55 (33)
Patients with acute thrombotic lesions	35/55 (64)
Patients with chronic disease	33/55 (60)
Acute on chronic lesion	23/55 (42)
SYNTAX score	29.4 ± 13.9
Procedural outcomes	
Patients with stent implanted	45/46 (98)
No. of stents/patient	2.7 ± 2.0
Intra-aortic balloon pump inserted	25/55 (45)

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Patient Characteristics and Time

TABLE 1 Patient Demographic Characteristics, Medical History, and Resuscitation Characteristics of the 62 Patients Meeting Early EMS Transport Criteria and the 170 Patients of the Historical Comparison Group

	Historical Comparison Group (n = 170)	University of Minnesota Refractory VF/VT Program Group (n = 62)
Male	124 (73.0)	44 (71.0)
Age, yrs	56 ± 7	58 ± 10
Medical history		
Diabetes	38 (22.0)	12 (19.0)
CAD	22 (13.5)	5 (9.0)
Hypertension	63 (37.0)	30 (48.0)
Hyperlipidemia	54 (32.0)	23 (36.0)
Smoking	47 (28.0)	14 (23.0)
Coronary artery bypass graft	NA	5 (9.0)
Congestive heart failure	NA	8 (13.0)
Resuscitation time intervals		
Time from 911 call to EMS arrival, min	7.2 ± 6.5	6.2 ± 4.6
Time from 911 call to CCL arrival, min	NA	58.0 ± 17.7
Time from 911 call to ECLS, min	NA	64.0 ± 13.2
Time to CCL entry on ECLS, min	NA	6.1 ± 1.8
CCL entry-to-balloon time, min	NA	12.0 ± 3.0

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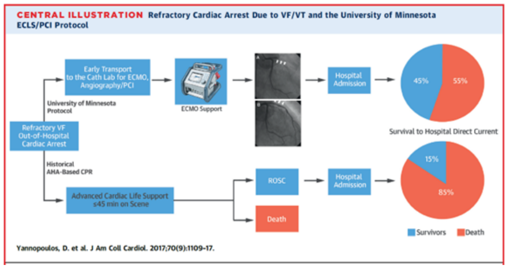
Survival Compared with Standard Care (ALPS)



- 28/62 (45%) functionally favorable survival
- 2/62 (3%) discharge with poor neurological function (ALPS = 5.7%)
- No life-threatening ECMO complications

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ECMO-facilitated Resuscitation versus Standard ACLS for Refractory VF Out-of-Hospital Cardiac Arrest THE ARREST TRIAL

Demetris Yannopoulos MD, Jason Bartos MD, PhD, Ganesh Raveendran MD, Emily Walser BSN, John Connett PhD, Thomas A Murray PhD, Gary Collins MS, Lin Zhang PhD Rajat Kalra MBChB, Marinos Kosmopoulos MD, Ranjit John MD, Andrew Shaffer MD, RJ Frascone MD, Keith Wesley MD, Marc Conterato MD, Michelle Biros MD, Tom P Aufderheide MD, MS

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Methods

- First prospective, randomized clinical trial of ECMO-facilitated resuscitation versus standard ACLS treatment (all prior: case series)
- Phase II, single center, intention-to-treat, safety and efficacy study
- Inclusion criteria
  - 18-75 with VT/VF OHCA, no ROSC after 3 shocks, LUCAS CPR, EMS estimated transfer < 30 minutes
- Trial blinded to EMS and outcome assessment; ICU protocolized
- The trial was terminated early by NHLBI after unanimous recommendation by the DSMB after first 30 patients were randomized by exceeding the pre-specified stopping criteria. (Posterior probability >0.986)

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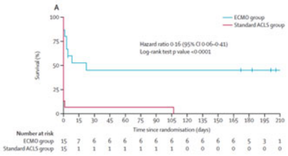
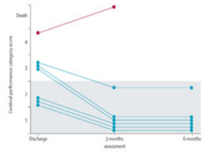
Outcome

- Survival to Hospital Discharge
  - ECMO: 6/14 (42.9%)
  - Standard ACLS: 1/15 (6.7%)



mRS Score

CPC Score



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THE LANCET

Advanced reperfusion strategies for patients with out-of-hospital cardiac arrest and refractory ventricular fibrillation (ARREST): a phase 2, single centre, open-label, randomised controlled trial

Demetris Yannopoulos, Jason Bartos, Ganesh Raveendran, Emily Walser, John Connett, Thomas A Murray, Gary Collins, Lin Zhang, Rajat Kalra, Marinos Kosmopoulos, Ranjit John, Andrew Shaffer, R J Frascone, Keith Wesley, Marc Conterato, Michelle Biros, Jakub Tolar, Tom P Aufderheide

Summary

Background Among patients with out-of-hospital cardiac arrest (OHCA) and ventricular fibrillation, more than half present with refractory ventricular fibrillation unresponsive to initial standard advanced cardiac life support (ACLS) treatment. We did the first randomised clinical trial in the USA of extracorporeal membrane oxygenation (ECMO)-facilitated resuscitation versus standard ACLS treatment in patients with OHCA and refractory ventricular fibrillation.

Methods For this phase 2, single centre, open-label, adaptive, safety and efficacy randomised clinical trial, we included adults aged 18–75 years presenting to the University of Minnesota Medical Center (MN, USA) with OHCA and refractory ventricular fibrillation, no return of spontaneous circulation after three shocks, automated cardiopulmonary resuscitation with a Lund University Cardiac Arrest System, and estimated transfer time shorter than 30 min. Patients were randomly assigned to early ECMO-facilitated resuscitation or standard ACLS treatment on hospital arrival by use of a secure schedule generated with permuted blocks of randomly varying block sizes. Allocation concealment was achieved by use of a randomisation schedule that required scratching off an opaque layer to reveal assignment. The primary outcome was survival to hospital discharge. Secondary outcomes were safety, survival, and functional assessment at hospital discharge and at 3 months and 6 months after discharge. All analyses were done on an intention-to-treat basis. The study qualified for exception from informed consent (21 Code of Federal Regulations 50.24). The ARREST trial is registered with ClinicalTrials.gov, NCT03880565.

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Center for Resuscitation Medicine, University of Minnesota Medical School, Minneapolis, MN, USA (Prof D Yannopoulos MD, J Bartos MD, Prof G Raveendran MD, E Walser BSN, R Kalra MBChB, M Kosmopoulos MD, Prof J Tolar MD); **Division of Cardiology, Department of Medicine** (Prof D Yannopoulos, J Bartos, Prof G Raveendran, E Walser, R Kalra, M Kosmopoulos), **and Division**

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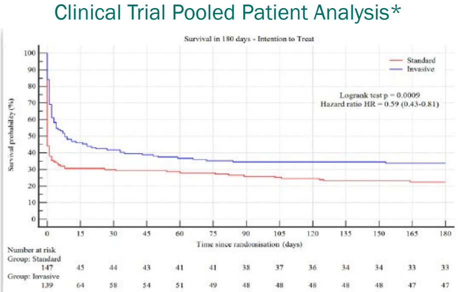
ARREST and Prague Prospective Randomized Clinical Trial Pooled Patient Analysis*



*Belohlavek, Yannopoulos, Aufderheide, et al. eClinicalMedicine. 2023 May 5;59:101988.

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What Have We Learned?

- These patients are treatable and salvageable .
- Average age of 58 (14% ≤ 39 years old) in the prime of their lives with reasonable expectation for continued quality and duration of life
- ECMO/ALPS: FF Survival (43%/7%, $p < 0.0001$)

Model	Odds Ratio	95% CI
Model 1: study (UMN-ECPR vs ALPS)	1.59	1.09–2.32
Model 2: model 1+CPR duration	39.77	18.62–84.90
Model 3: model 2+age, sex, race, witnessed arrest, bystander CPR, and public location	20.80	8.65–50.03

- Poor survival: ECMO = 3.0%; Standard care = 5.7%
- Cause: Severe CAD with near total occlusion of all blood flow to the heart.
- As such, continued treatment with standard care is unlikely to significantly improve survival without addressing reversal of the underlying cause

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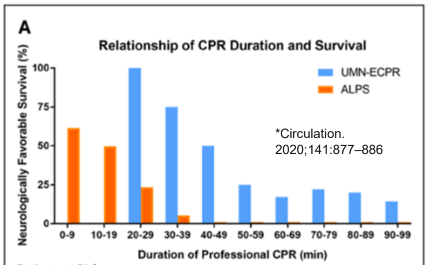
CPR Duration and FF Survival (ECMO vs ALPS)*



*Circulation. 2020;141:877–886

Patients at Risk

Time (min)	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99	Total
UMN-ECPR	0	0	8	12	20	36	35	27	15	7	160
ALPS	70	151	102	95	99	69	29	11	3	7	636

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Event during ECMO Rounds

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A New Understanding of the Process of Death

- Death is not an event; it is a process
- Any process can be successfully interrupted and reversed
- How long is the process of death?
- Most medical professionals/public believe that death is inevitable after 3-4 minutes without oxygen
- Is there scientific evidence for this belief system?
- Is it true?

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ARCHIVES OF NEUROLOGY AND PSYCHIATRY 1940

TEMPORARY ARREST OF THE CIRCULATION TO THE CENTRAL NERVOUS SYSTEM

II. PATHOLOGIC EFFECTS

LAURENCE M. WEINBERGER, M.D.
MARY H. GIBBON
AND
JOHN H. GIBBON Jr., M.D.
PHILADELPHIA

In a preceding article,[1] the symptomatic effects of temporary complete interruption of the blood flow to the central nervous system were reported. The following report deals with the pathologic changes occurring in the central nervous system of 12 cats subjected to varying periods of circulatory arrest and killed from two days to six weeks later. The material to be presented is thought to be of interest for two reasons. First, it deals almost exclusively with the late permanent neuropathologic changes, and not with the earlier evidences of injury,

SUMMARY

1. Permanent pathologic lesions may occur in the cerebral cortex of the cat after complete arrest of the circulation for three minutes and ten seconds.

2. Frank necrosis and softening of the cortex have been observed after circulatory interruption for three minutes and twenty-five seconds.

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CARDIAC RESUSCITATION—COLE AND CORDAY J.A.M.A., August 11, 1956

FOUR-MINUTE LIMIT FOR CARDIAC RESUSCITATION

Seymour L. Cole, M.D.
and
Eliot Corday, M.D., Los Angeles

Cardiac arrest is considered to have occurred when the heartbeat is no longer strong enough to be of hemodynamic significance. Since it results in failure of oxygen transport, every case of cardiac arrest is an emergency calling for immediate action, because the cells of the cerebral cortex cannot survive long after their oxygenated blood supply has been interrupted. Depending on the effectiveness of resuscitative efforts within a very short period, the individual may recover completely, die in a few hours, or live longer in varying degrees of a decerebrate state.

The urgency of the problem became evident when

• Duration of cardiac arrest and the degree of cardiac and cerebral recovery were studied in 132 patients in whom cardiac arrest had occurred during anesthesia and surgery and postoperatively. It was found that 53 had not been revived and that 44 died after varying periods of survival. Complete recovery occurred in 33 patients, and in all of these cases resuscitative measures were found to have been started within four minutes after the cardiac arrest was noted. Two patients who survived despite a delay of more than four minutes have a cerebral impairment that is probably permanent.

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ARTICLE

https://doi.org/10.1038/s41586-019-1099-1

Restoration of brain circulation and cellular functions hours post-mortem

Zvonimir Vrselja[1,2,18], Stefano G. Daniele[1,2,3,18], John Silbereis[1,2], Francesca Talpo[1,2,4], Yury M. Morozov[1,2], André M. M. Sousa[1,2], Brian S. Tanaka[5,6,7], Mario Skarica[1,2], Mihovil Pletikos[1,2,8], Navjot Kaur[1,2], Zhen W. Zhuang[9], Zhao Liu[9,11], Rafeed Alkawadri[6,10], Albert J. Sinusas[9,11], Stephen R. Latham[12], Stephen G. Waxman[5,6,7] & Nenad Sestan[1,2,13,14,15,16,17]✉

The brains of humans and other mammals are highly vulnerable to interruptions in blood flow and decreases in oxygen levels. Here we describe the restoration and maintenance of microcirculation and molecular and cellular functions of the intact pig brain under ex vivo normothermic conditions up to four hours post-mortem. We have developed an extracorporeal pulsatile-perfusion system and a haemoglobin-based, acellular, non-coagulative, echogenic, and cytoprotective perfusate that promotes recovery from anoxia, reduces reperfusion injury, prevents oedema, and metabolically supports the energy requirements of the brain. With this system, we observed preservation of cytoarchitecture; attenuation of cell death; and restoration of vascular dilatory and glial inflammatory responses, spontaneous synaptic activity, and active cerebral metabolism in the absence of global electrocorticographic activity. These findings demonstrate that under appropriate conditions the isolated, intact large mammalian brain possesses an underappreciated capacity for restoration of microcirculation and molecular and cellular activity after a prolonged post-mortem interval.

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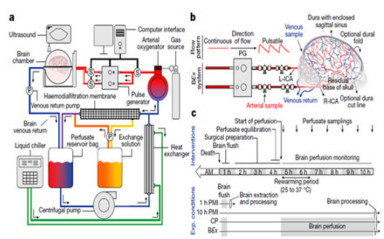

Fig. 1 | BEx perfusion system and experimental workflow. a, Simplified schematic of the closed-circuit perfusion device. S, sensor; P, pump. **b**, Connection of the porcine brain to the perfusion system via arterial lines. The pulse generator (PG) transforms continuous flow to pulsatile perfusion. Ports for arteriovenous sampling are shown. In this preparation, the dura can be carefully cut and folded medially to access the brain for experimentation; surgical care is taken to ensure that cortical bridging veins remain intact. R-ICA and L-ICA, right and left internal carotid arteries; **c**, Schematic depicting the experimental workflow and conditions. AM, ante-mortem.

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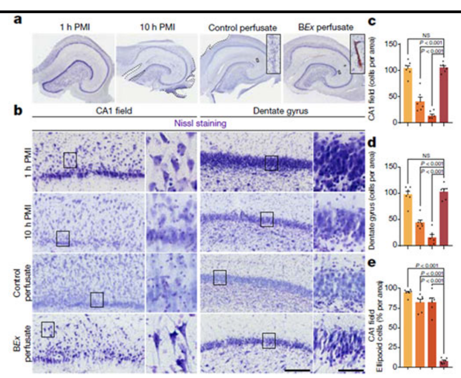

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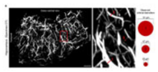
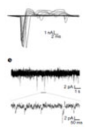
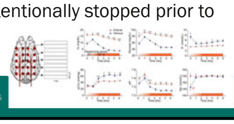
Proven Findings



- Vascular function was restored and maintained
- Cell death stopped
- Nerves and synapses restored with electrochemical function
- Glial cells preserved
- Inflammatory function restored
- Global cerebral metabolism restored and maintained
- Brains anesthetized and study intentionally stopped prior to restoration of consciousness





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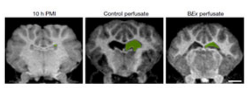
Conclusions



- Cell death in the post mortem brain occurs over a longer time window than widely thought
- Post mortem cells retain the capacity for restoration with the appropriate intervention(s) in the fully intact brain
- Global cerebral metabolism can be restored multiple hours after death

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Clinical Implications

- Declaration of Death
  - Brain death (2%)
  - Clinical declaration of death (98%)
    - Functional definition
    - No signs of life, exhausted all known effective interventions, and have nothing further to offer the patient
    - Reasonable and appropriate
    - But….they are not dead!
  - New definition of death: Irreversible biological cell death
    - When irreversible biological death occurs is unknown, but occurs at least > 4 hours (and probably much longer than 4 hours) following clinical declaration of death
- The window of opportunity for future effective resuscitation intervention is much longer than previously thought!

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ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Special Issue: *Surviving Cardiac Arrest*

Review

Enhancing cardiac arrest survival with extracorporeal cardiopulmonary resuscitation: insights into the process of death

Tom P. Aufderheide,[1] Rajat Kalra,[2,3] Marinos Kosmopoulos,[2] Jason A. Bartos,[2,3] and Demetris Yannopoulos[2,3]

[1]Department of Emergency Medicine, HUB for Collaborative Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin. [2]Center for Resuscitation Medicine, University of Minnesota Medical School, Minneapolis, Minnesota. [3]Cardiovascular Division, University of Minnesota, Minneapolis, Minnesota

Address for correspondence: Tom P. Aufderheide, MD, MS, FACEP, FACC, FAHA, Department of Emergency Medicine, HUB for Collaborative Medicine, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226.
taufderh@mcw.edu

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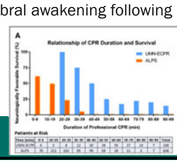
No Physician-Directed WLST Until Definitive Death Has Occurred

- Patients are salvageable much longer than previously recognized. Functionally favorable survival:
  - Routine 90-99 minutes CPR; no absolute limit identified
- Current ICU neuro-prognostication practice becomes a self-fulfilling prophesy, inserts ascertainment bias, and undermines confidence in the validity of current practice
  - Average time to first neurological awakening: 5.7 ± 0.8 days
  - Longest time to first neurological awakening with functionally favorable survival: 32 days!
- Resuscitation medicine knows little about the process of cerebral awakening following ischemic insult
  - Cardiac recovery: ROSC
  - Cerebral recovery: electrical activity after known duration of coma



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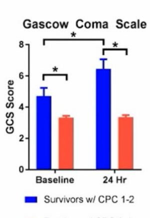
Neurologic Exam

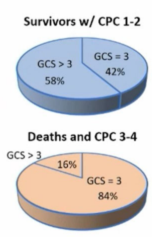
Posturing: unhelpful

Tremors: unhelpful

Roving gaze: unhelpful

Inappropriate Tachypnea: common with good outcomes





Brainstem Reflexes: 36% of patients who died or had CPC 3-4 had no brainstem reflexes at 24 Hrs; All survivors had intact brainstem reflexes

Bartos et al., Unpublished

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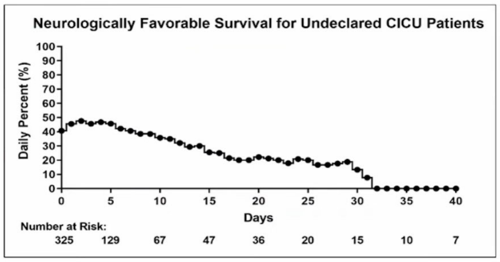
Survival Requires Patience



Bartos, unpublished data

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Summary

- The "3-minutes without oxygen" belief system is no longer supported by scientific evidence. That 80-year old myth should be aggressively discarded.
- The process of death and resilience of the brain to recover from ischemic insult is much longer than generally recognized
- This evidence extends the window of opportunity for new and more effective resuscitation interventions in the future

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Summary

- There is a critical need for resuscitation science to focus on the brain and develop effective neuroprotective strategies
- Important ethical considerations of this new reality need to be addressed.
- Moving forward, we need to recalibrate our entire healthcare system approach to cardiac arrest following prolonged ischemic insult.
- Our understanding of the potential salvageability of patients, the process of death, and cerebral awakening is just beginning, and we have a lot to learn!

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Thank you!

- ECMO Program Lecture: https://www.youtube.com/watch?v=J2Bz50gXH48

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