Hypothermia in Emergency Medicine: Treating Post Cardiac Arrest Injury

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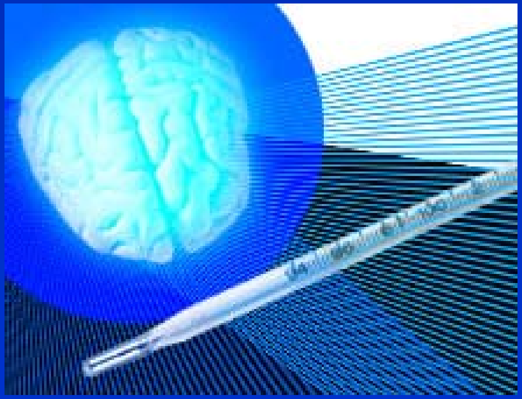


Conflict of interest disclosures:

- Research funding from NIH, DOD
- Preclinical hypothermia work includes patents for micro-particulate ice slurry

Other disclosures:

- Mention of non-FDA approved devices for hypothermia

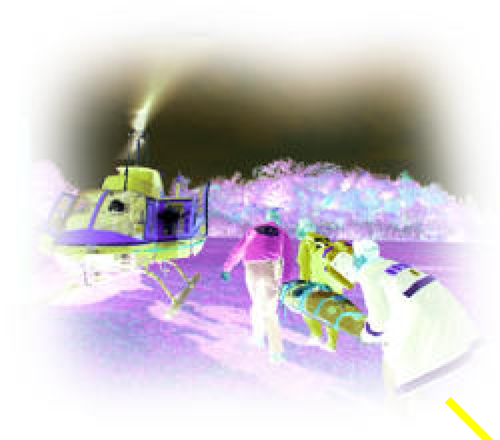
Cooling and ischemia/reperfusion

- **May 20, 1999, 18:20**
- 29yo F skier fell down gully, wedged under ice and water
- **18:27** "911 call" to Narvik Hospital
- **19:00** Pt stopped moving
- **19:39** Rescue team arrives

Lancet 355:375-376,2000.

Cooling and ischemia/reperfusion

- **19:56** air ambulance arrives
- **21:10** CPR continues, arrive at Tromso University Hospital
- **21:50** core temp 14.4°C, full cardiopulmonary bypass started, temp decreases to 13.7 °C
- **22:00** asystole converts to VF
- **22:15** spontaneous pulse esophageal temp 31.5°C



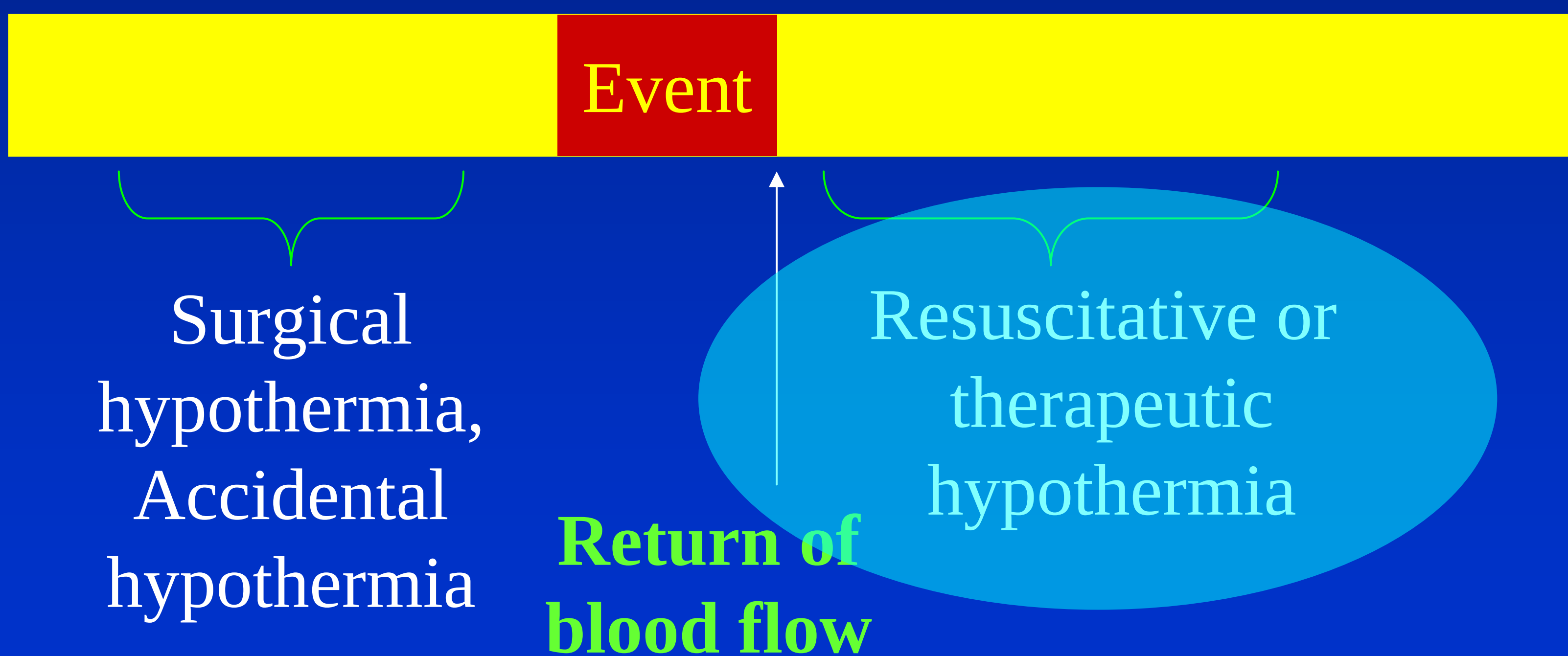
Lancet 355:375-376,2000.

Cooling and ischemia/reperfusion

- **5 days** ECMO
- **28 days** ICU stay
- **35 days** extubated
- **5 months** residual partial paresthesias, has resumed hiking and skiiing

Lancet 355:375-376,2000.

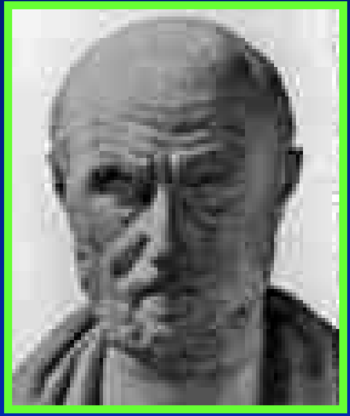
Hypothermia and clinical ischemia/reperfusion



History of Therapeutic Hypothermia

Very old concept:

Hippocrates (450 BC) – packed injured patients in snow, ? improved survival



Baron Larrey, 1814 (battlefield surgeon)

Cold acts on the living parts… [which] may remain… in [a] state of asphyxia without losing their life

Modern History of Therapeutic Hypothermia

Benson et al, 1959, showed benefit
From hypothermia after cardiac arrest

Cooling fell out of favor for several decades…

Safar pioneers concept
of induced hypothermia as
treatment for cardiac arrest,
extensive animal modeling

Hypothermia: clinical treatment for post-cardiac arrest injury and death

HACA (2002)

The New England Journal of Medicine

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INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

Bernard (2002)

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

STEPHEN A. BERNARD, M.B., B.S., TIMOTHY W. GRAY, M.B., B.S., MICHAEL D. BUIST, M.B., B.S.,
BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.SC.

Cooling methods

- Surface cooling

Ice bags in addition
to cooling blanket
required in about
70% of pts
to reach target temp

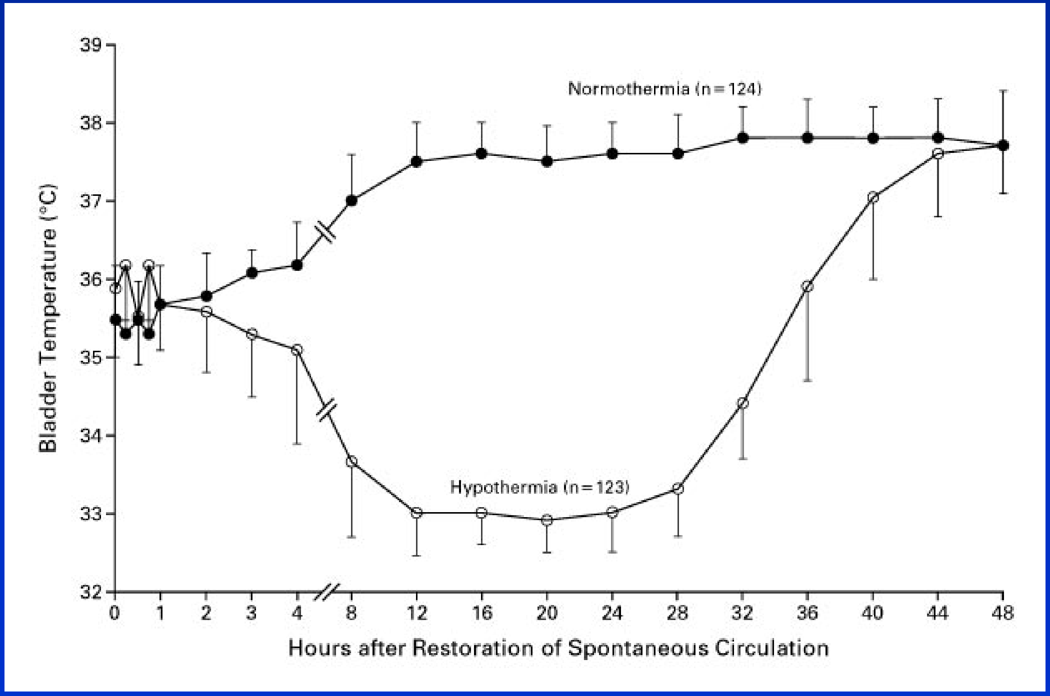


Table 1. Base-Line Characteristics of the Patients.

Characteristic	Normothermia (N=138)	Hypothermia (N=137)
Age — yr		
Median	59	59
Interquartile range	49–67	51–69*
Female sex — no./total no. (%)	32/138 (23)	33/137 (24)
Medical history — no./total no. (%)		
Diabetes	26/138 (19)	11/135 (8)
Coronary heart disease	59/138 (43)	43/135 (32)
Cerebrovascular disease	11/138 (8)	10/135 (7)
NYHA class III or IV†	16/132 (12)	14/130 (11)
Location of cardiac arrest — no./total no. (%)		
Home	70/138 (51)	69/135 (51)
Public place	53/138 (38)	48/135 (36)
Other‡	15/138 (11)	18/135 (13)
Arrest witnessed — no./total no. (%)§	136/138 (99)	134/137 (98)
Presumed cardiac origin of arrest — no./total no. (%)§	135/138 (98)	135/137 (99)
Ventricular fibrillation or pulseless ventricular tachycardia — no./total no. (%)§	132/138 (96)	133/137 (97)
Basic life support provided by bystander — no./total no. (%)	68/138 (49)	59/137 (43)
Interval between collapse and restoration of spontaneous circulation — min¶		
Median	22	21
Interquartile range	17–33	15–28
Total epinephrine dose — mg		
Median	3	3
Interquartile range	1–6	1–5*
Hypotension after resuscitation — no./total no. (%)	68/138 (49)	75/137 (55)
Subsequent nonfatal arrest — no./total no. (%)	11/138 (8)	15/137 (11)
Thrombolysis after resuscitation — no./total no. (%)	24/133 (18)	27/135 (20)

*Data were not available for two patients.

†NYHA denotes New York Heart Association.

‡Other locations included a physician's office, the workplace, and the hospital.

§Although this was a criterion for inclusion in the study, in a few cases, the initial information was incorrect.

¶Data were not available for three patients in the normothermia group and four in the hypothermia group.

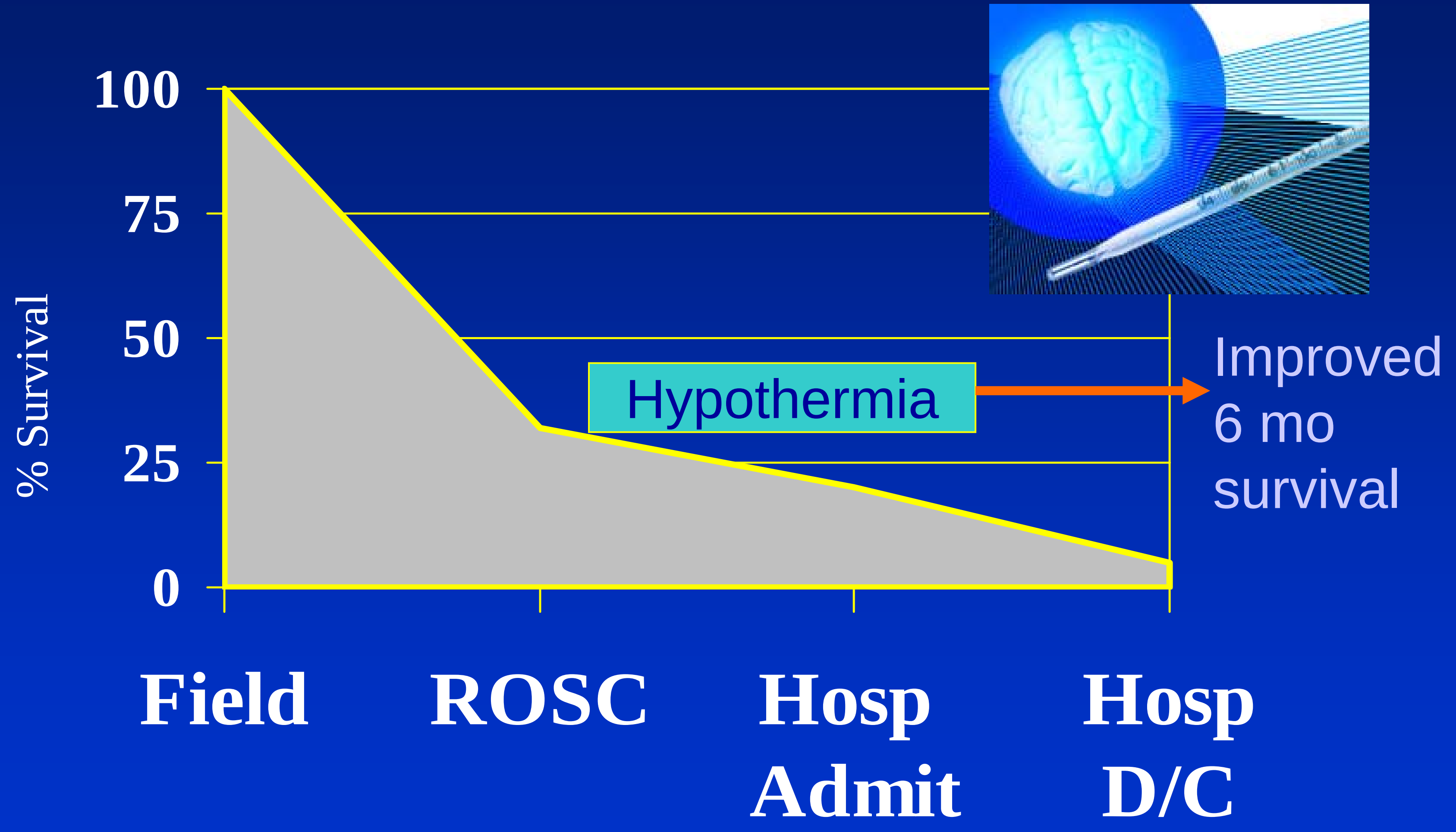
HACA Outcomes

	Normothermia (%)	Hypothermia (%)	RR (95% CI)	P value
At 6 months…				
Favorable Neuro	54/137 (39%)	75/136 (55%)	1.4 (1.08-1.81)	0.009

- NNT ~ 6 patients
- More DM/CAD in controls
- ~20% of patients received thrombolysis (uncommon in U.S.)

Post cardiac arrest survival is poor

Therapeutic hypothermia only effective tx known



Weil and Tang ed. 1999, CPR

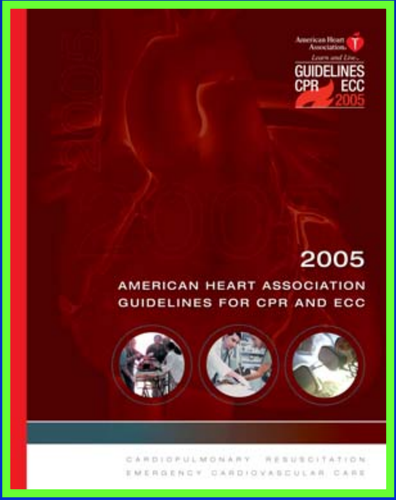
AHA Guidelines for Therapeutic Hypothermia

Existing guideline, practice or training activity:

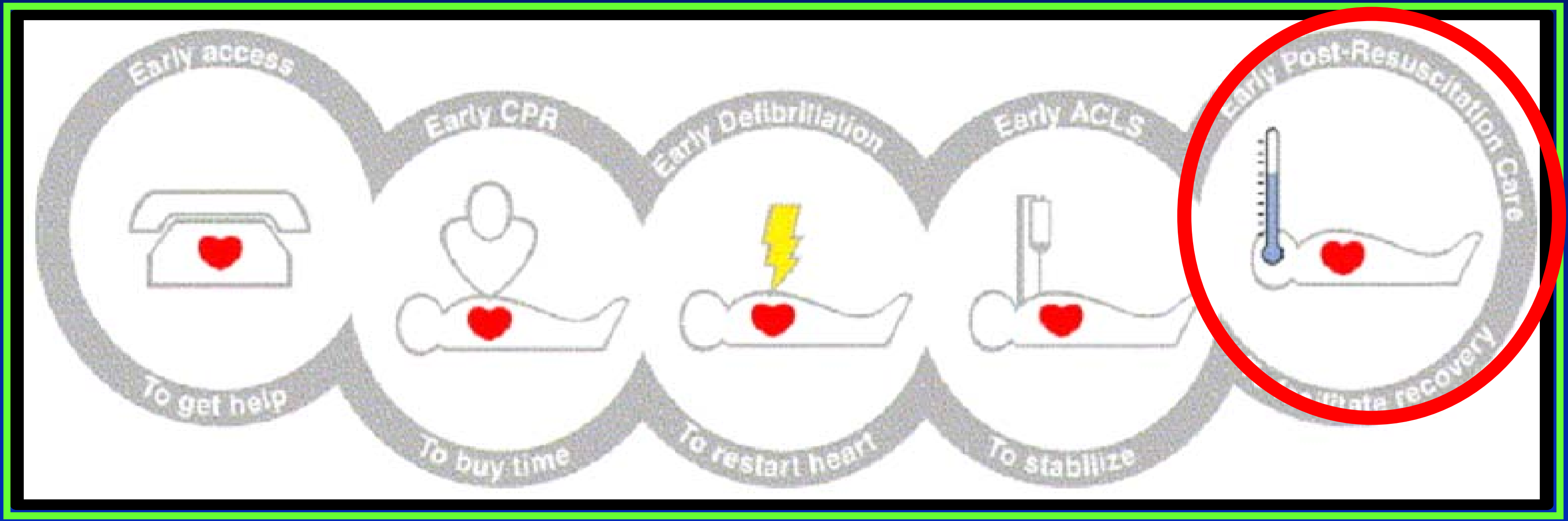
G2000:
Hemodynamically stable patients who develop a mild degree of hypothermia (>33°C) spontaneously after cardiac arrest should not be actively warmed. Mild hypothermia may be beneficial to neurological outcome and is likely to be well tolerated. However, hypothermia should not be induced actively after resuscitation from cardiac arrest.

ILCOR Advisory statement (2003):
Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34°C for 12-24 hrs when the initial rhythm was ventricular fibrillation (VF).
Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrests.

American Heart Association: Guidelines 2005 Recommendation



Consensus 2005
"Chain of Survival"



- Cooling attenuates multi-organ dysfunction
- Begin cooling as EARLY as possible
- Class IIa: Comatose out-of-hospital VF arrest
- Class IIb: Other rhythms and In-hospital Cardiac Arrest

Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest*

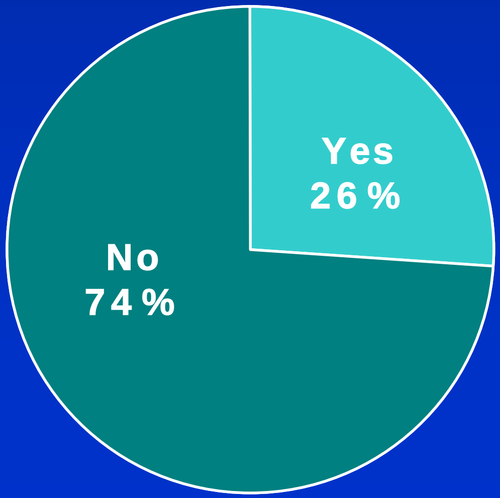
Raina M. Merchant, MD; Jasmeet Soar, MD; Markus B. Skrifvars, MD, PhD; Tom Silfvast, MD, PhD; Dana P. Edelson, MD; Fawaz Ahmad, BA; Kuang-Ning Huang; Monica Khan; Terry L. Vanden Hoek, MD; Lance B. Becker, MD; Benjamin S. Abella, MD, MPhil

Critical Care Medicine Epub June 2006

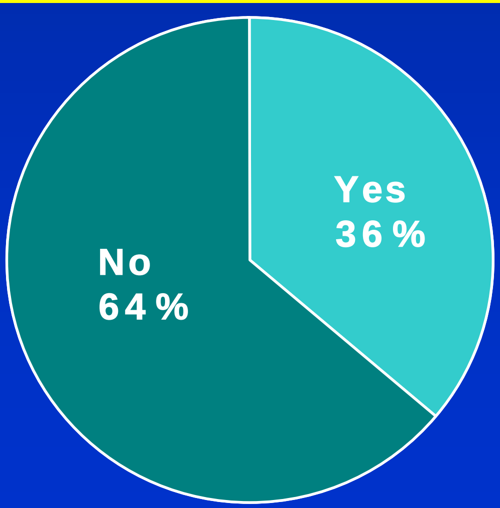
Web-based survey of
US and non-US physicians, May 2005
13,272 reached physicians, 2248 responded (17%)

Post-arrest cooling?

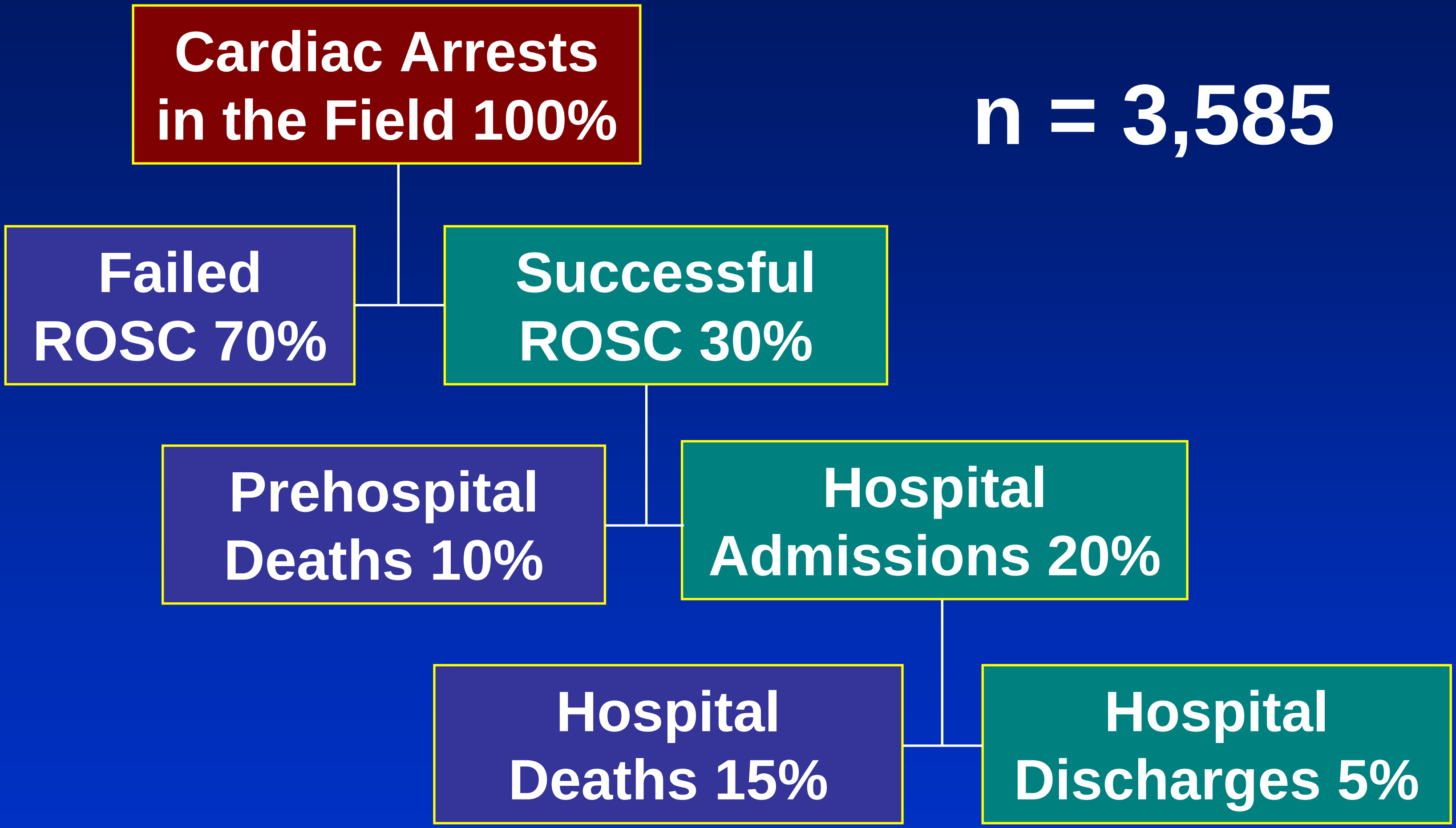
US physicians



Non-US physicians



Post-Cardiac Arrest Injury and the Heart



n = 3,585

Data compiled from studies reported by Brown CG (*N Engl J Med* 1992;327,1051), Kellermann AL (*JAMA* 1993;270:1433), and Lombardi G (*JAMA* 1994;271:678). ROSC = Restoration of spontaneous circulation.

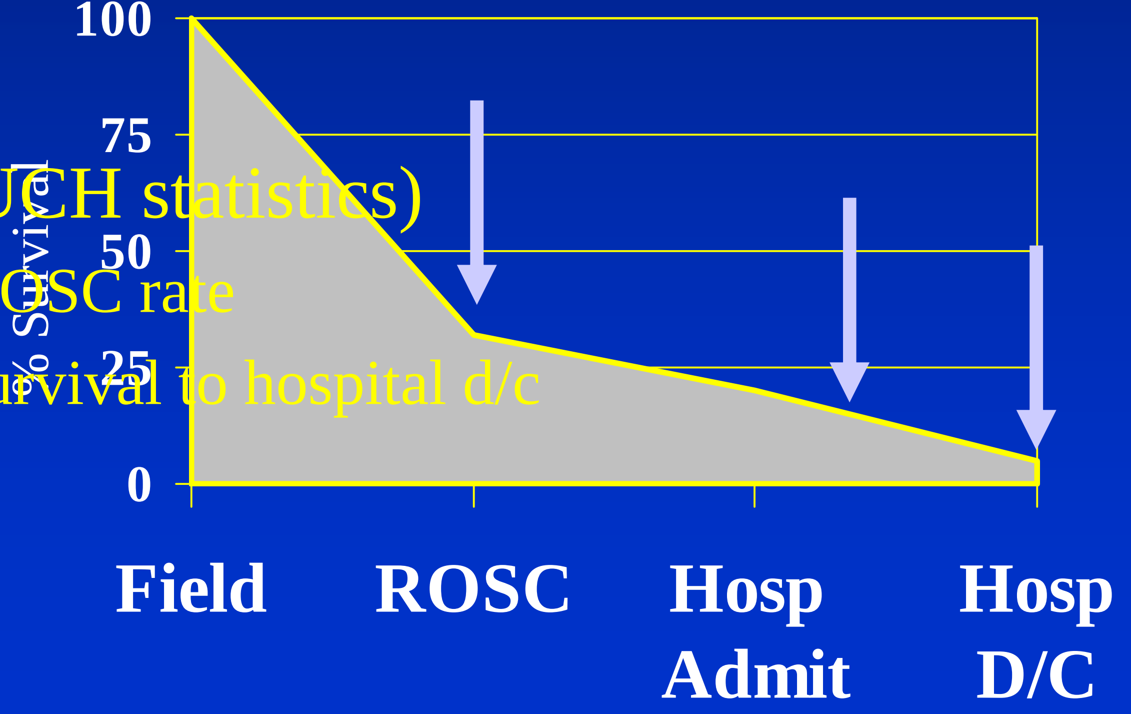
Gazmuri, Weil and Tang ed. 1999, Cardiopulmonary Resuscitation

Post Cardiac Arrest Survival is Poor

Post-ROSC Mortality is Significant

- Out-of-Hospital Cardiac Arrest
  - 30% ROSC rate
  - 10% survive 24h
  - 4% survive to hospital d/c

- IHCA (UCH statistics)
  - 52% ROSC rate
  - 18% survival to hospital d/c



Weil and Tang ed. 1999, CPR

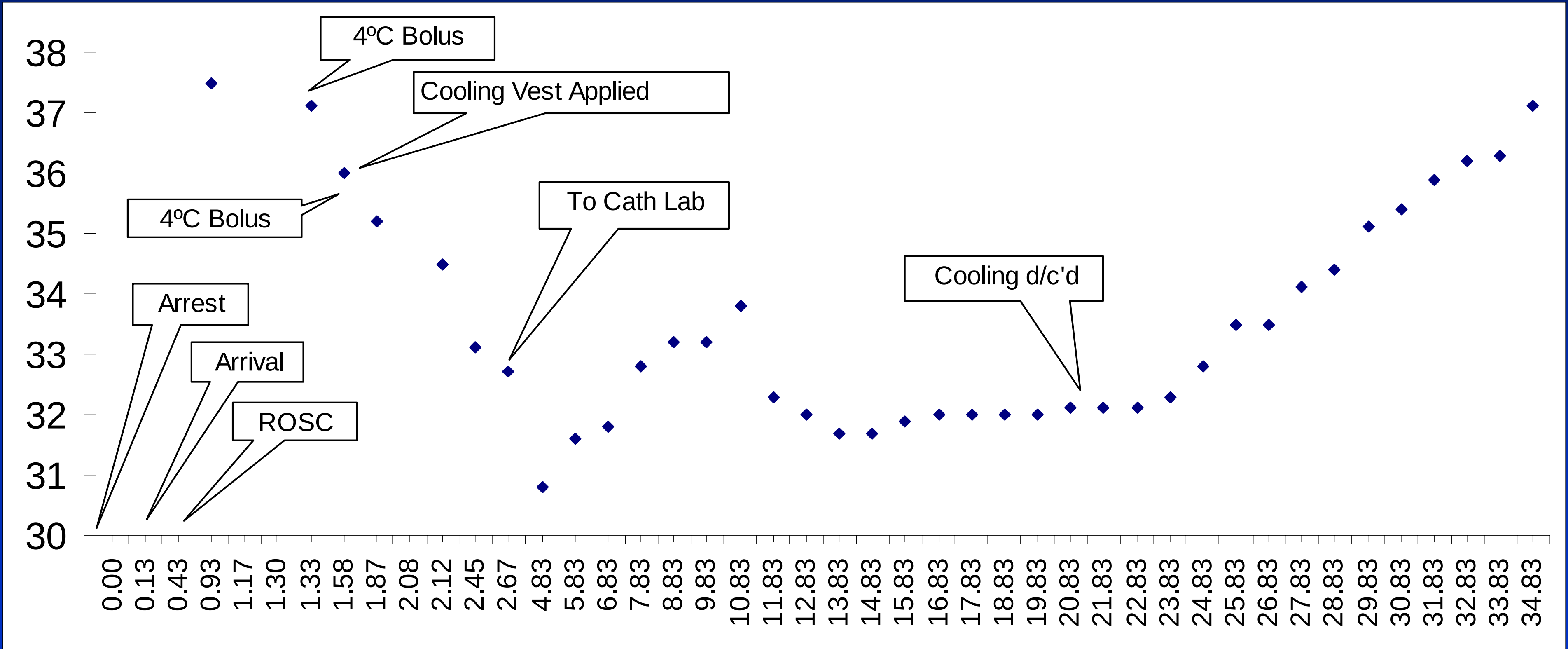
Clinical Case of Cardiac Arrest

- 02/8/07, Outside the hospital at 67th & King Drive
  - 52y woman collapses in passenger seat of private auto:
  - Friend drives her to the hospital
  - Triage nurse alerted, finds patient unresponsive in car
  - Patient transported inside the ER
- 2118: Ventricular Fibrillation
  - CPR initiated, IVs established, patient intubated
- 2122: Defibrillation at 200J

Clinical Case of Cardiac Arrest (con't)

- 2136: Return of Spontaneous Circulation (ROSC)!
  - After 3 rounds of epinephrine/atropine, vasopressin, amiodarone
  - 11 documented defibrillation attempts
- 2220: 1st liter 4ºC NS infused, rectal T=37.5ºC
- 2230: 2nd liter chilled saline, T= 37.5ºC

Core Temperature



Clinical Case of Cardiac Arrest (con't)

- Cardiac Catheterization Suite
  - Findings: Clean coronary arteries
  - Balloon pump placed
- Post-Resuscitation Syndrome:
  - Prolonged cardiogenic shock
  - Acute Renal Failure
  - Comatose x 5 days
- Extubated ~ Hospital Day 6
- Began conversing with family after 1 week, discharged home

Clinical Case Discussion

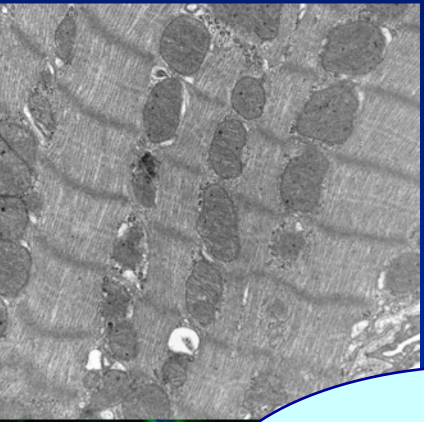
- This patient demonstrated both early (cardiac) and later (neurological) post-cardiac arrest injury.
- At many steps along the way, this patient could have been pronounced “dead” by standard practice.
- Hypothermia induction within 1 hr of ROSC was associated with protection despite 40 min ischemia! (other factors likely include quality CPR)
- Learning how hypothermia “works” could significantly improve post-cardiac arrest care.

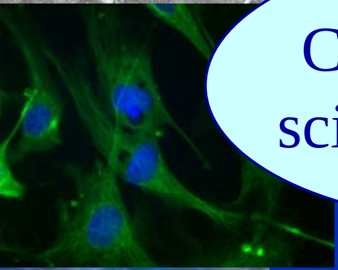
Translational Research of Hypothermia

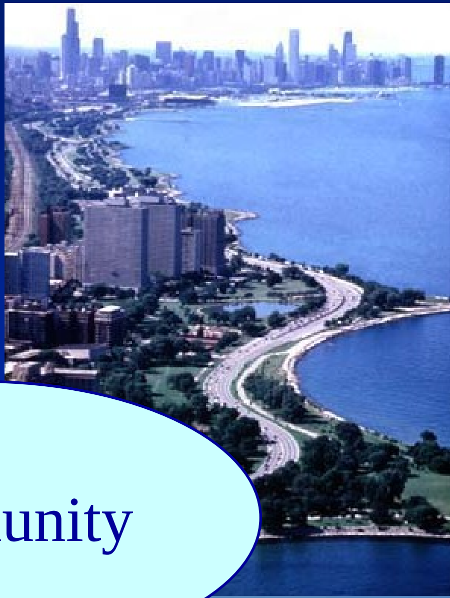
How to translate between laboratory and patient?

Optimal timing?

Mechanism of action?





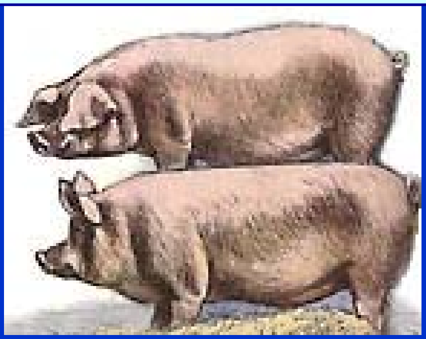


Cellular basic science research

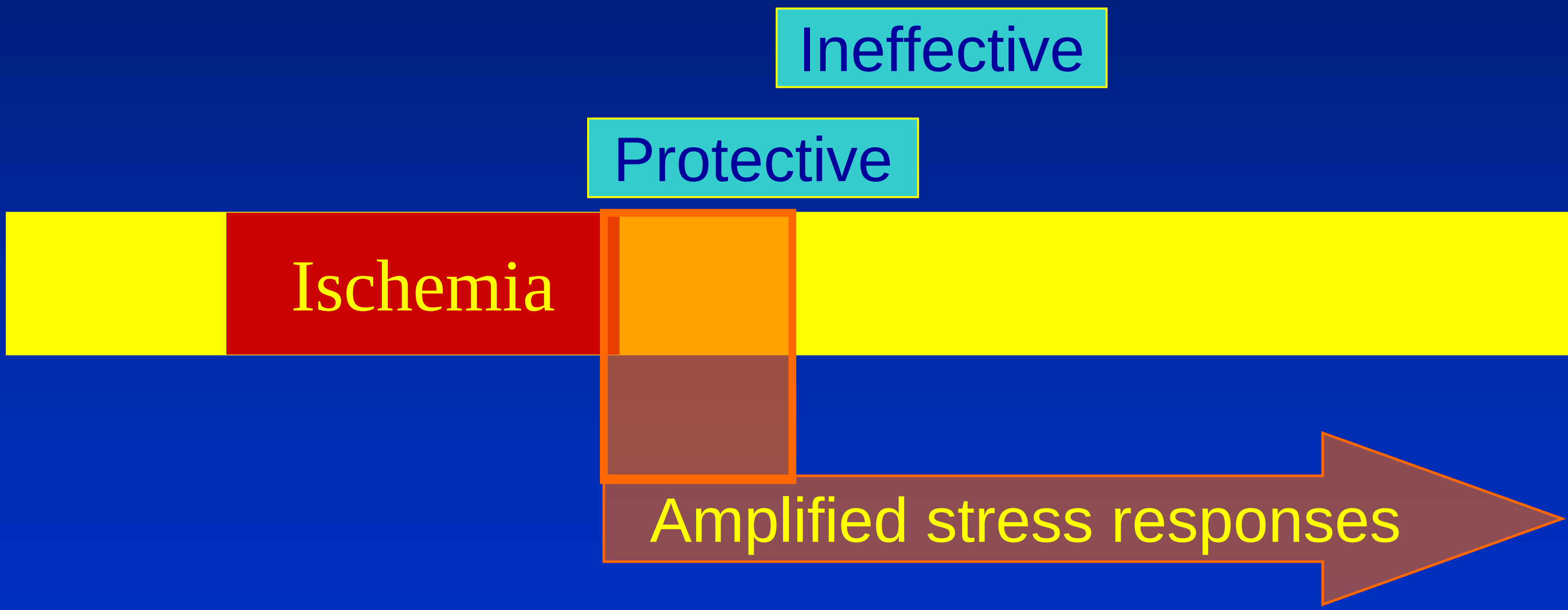
Translational research

Community

Bioengineering & Biotechnology

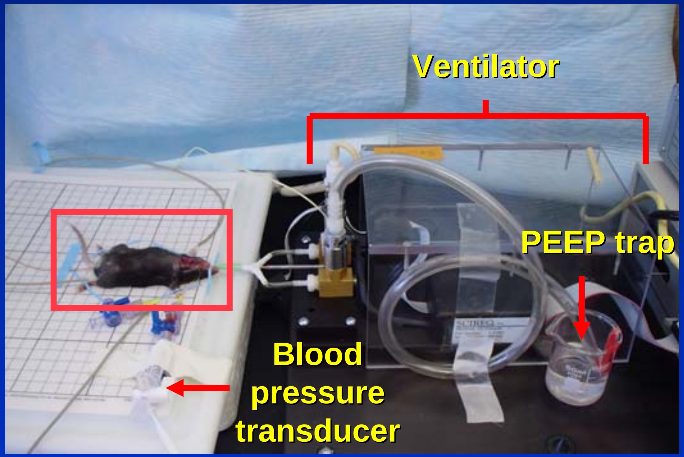


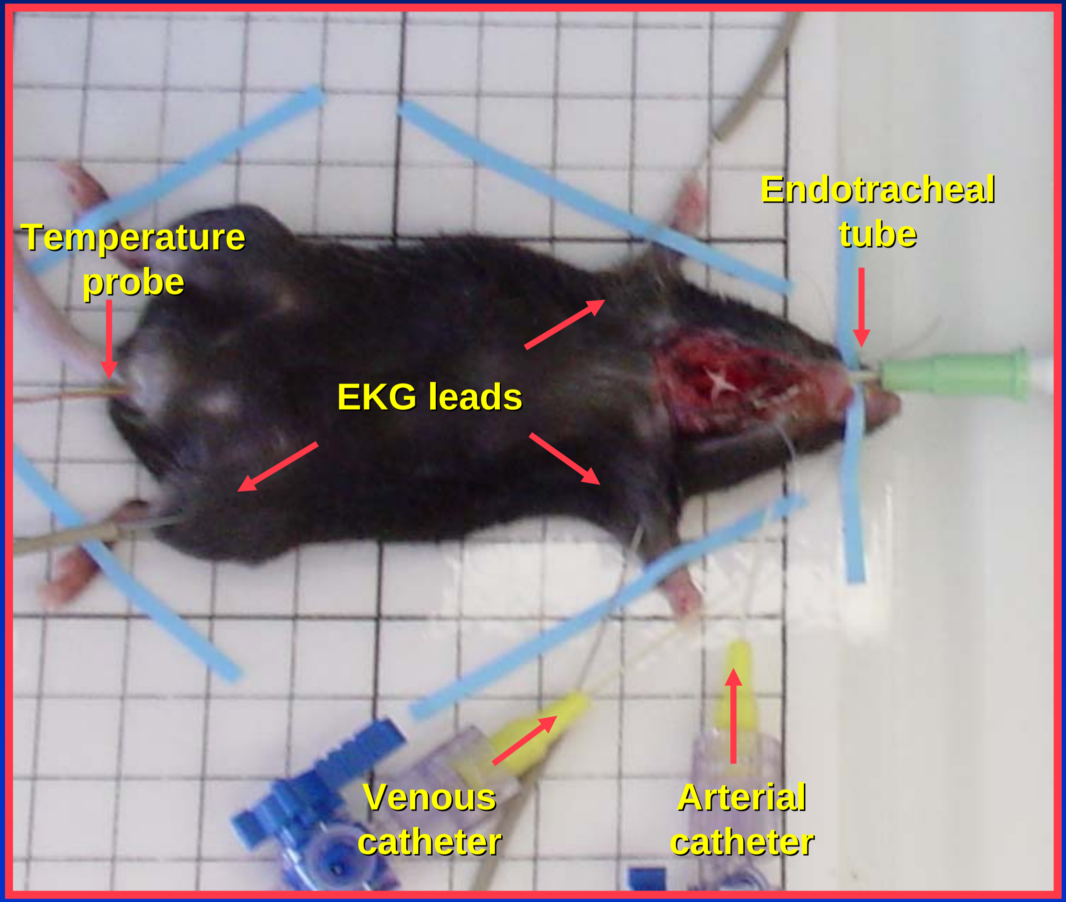
Therapeutic hypothermia and cardiac arrest in the laboratory: earlier cooling is better



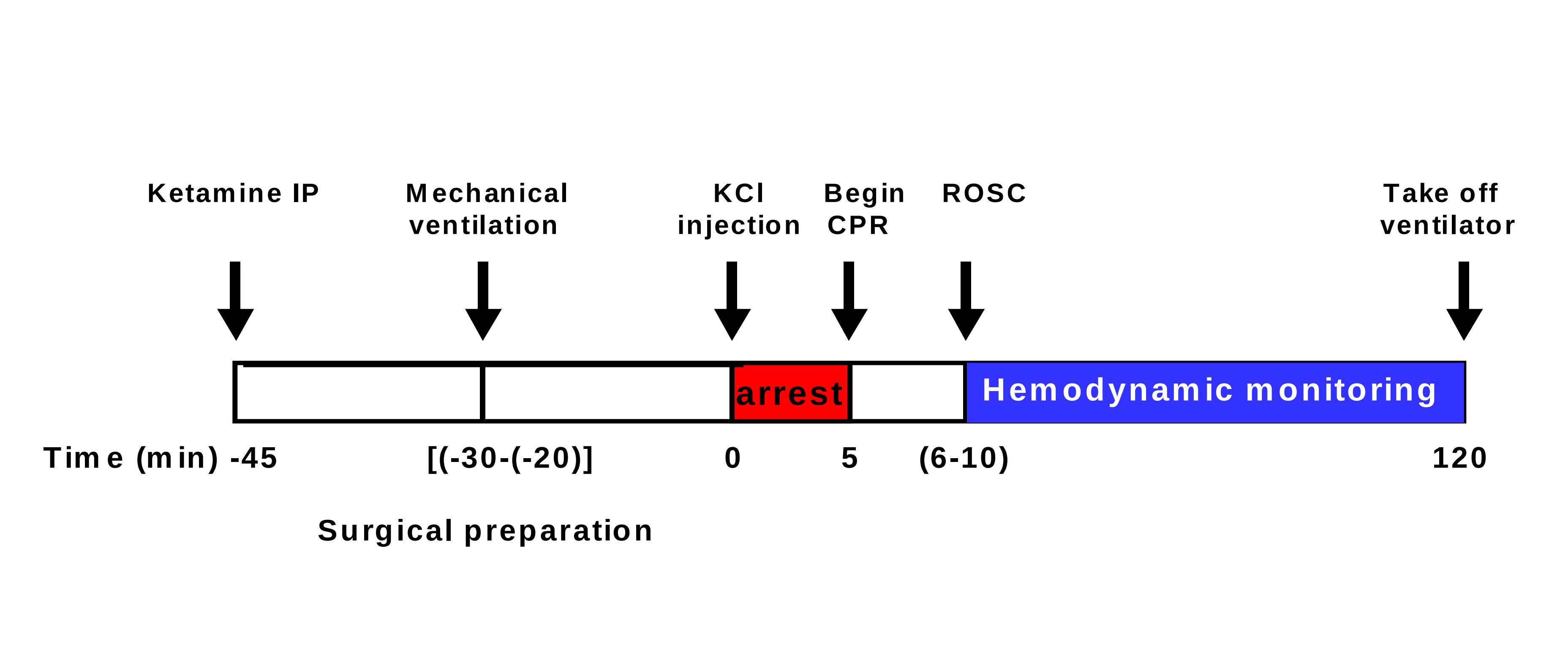
Suggests a critical window of opportunity to affect post-resuscitation outcomes affecting BOTH heart and brain

Mouse Model of Cardiac Arrest



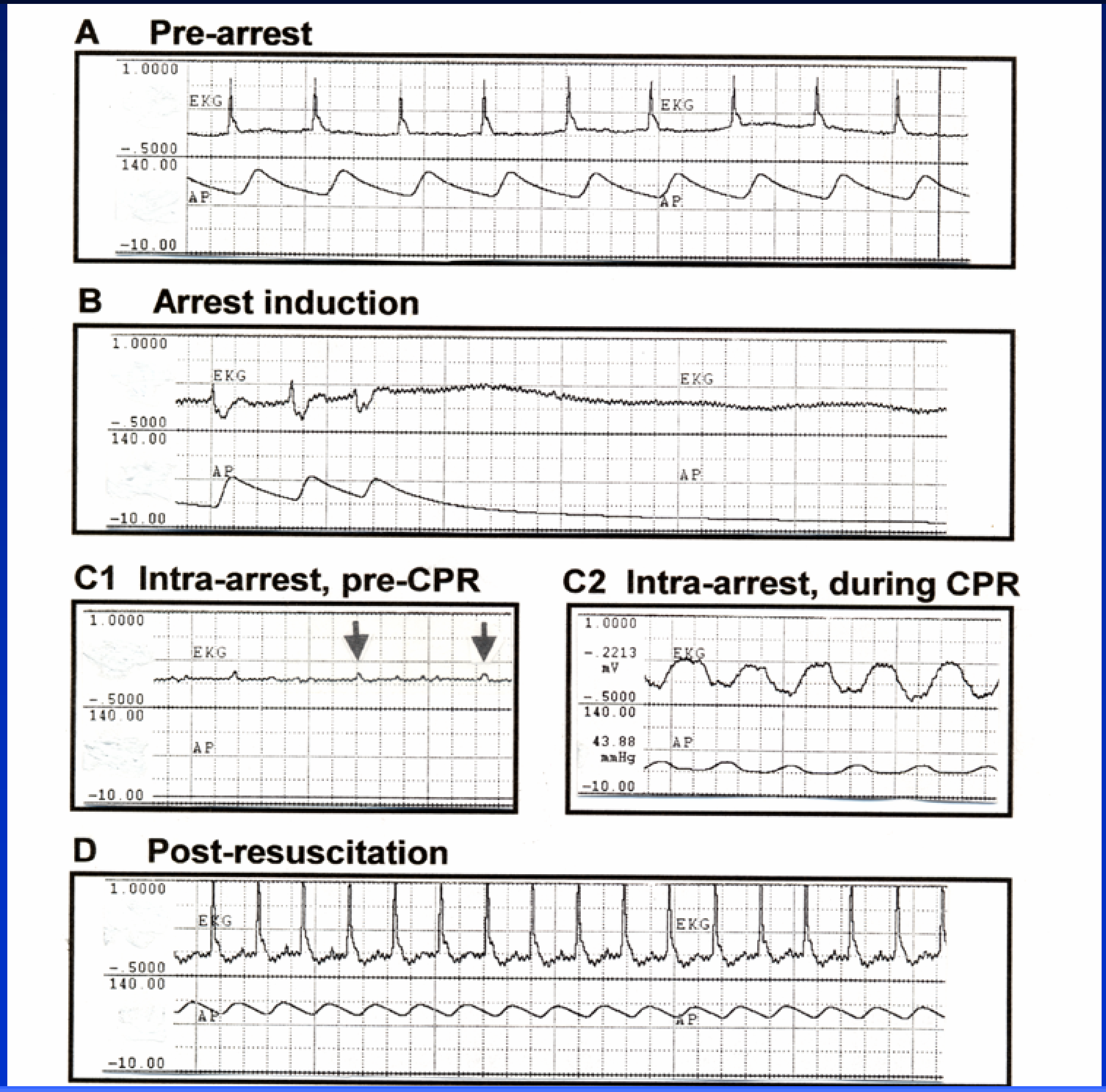


Whole body ischemia/reperfusion during mouse cardiac arrest

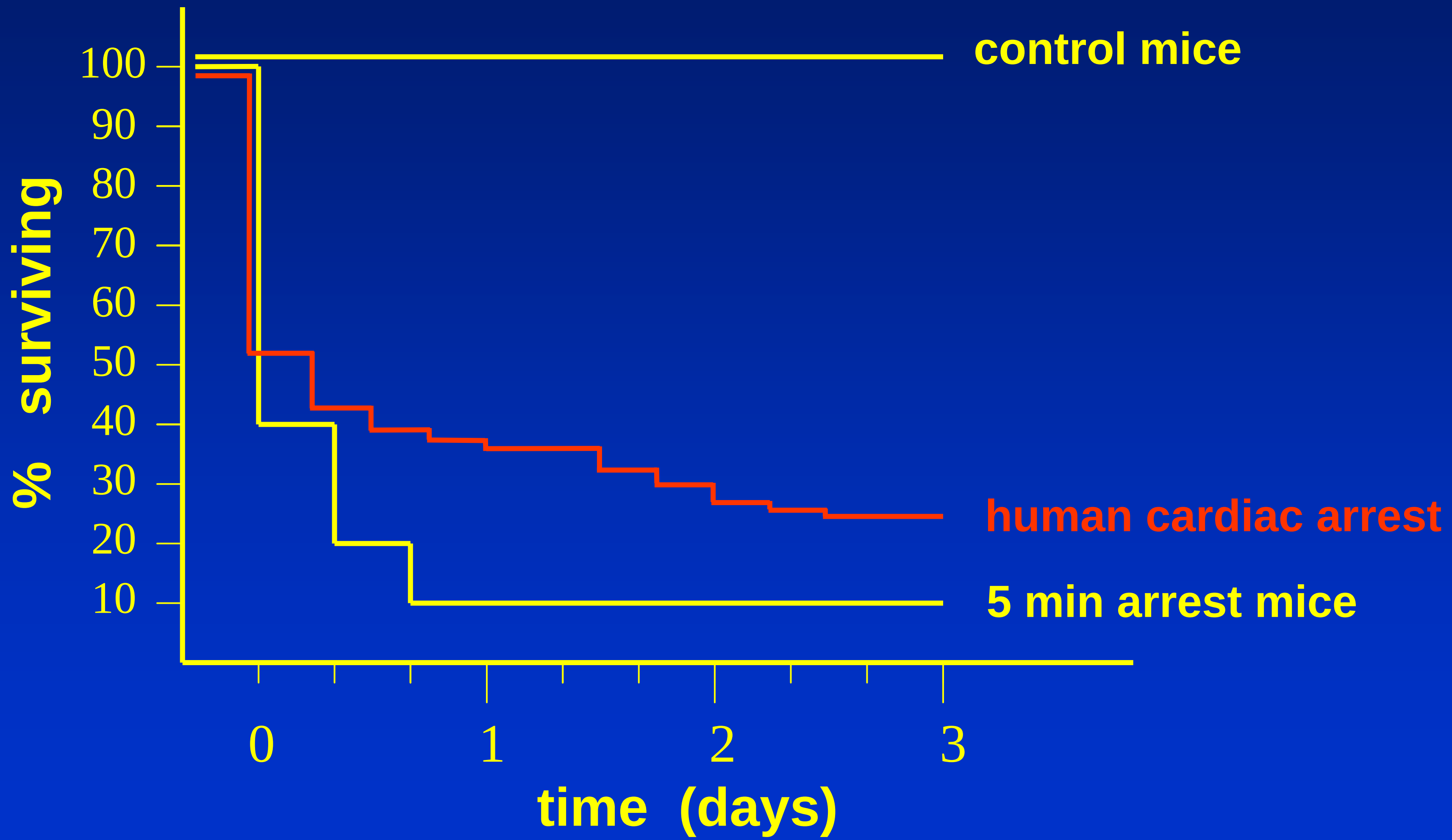


Abella et al. Circulation. 2004;109:2786-2791

EKG tracings during protocol

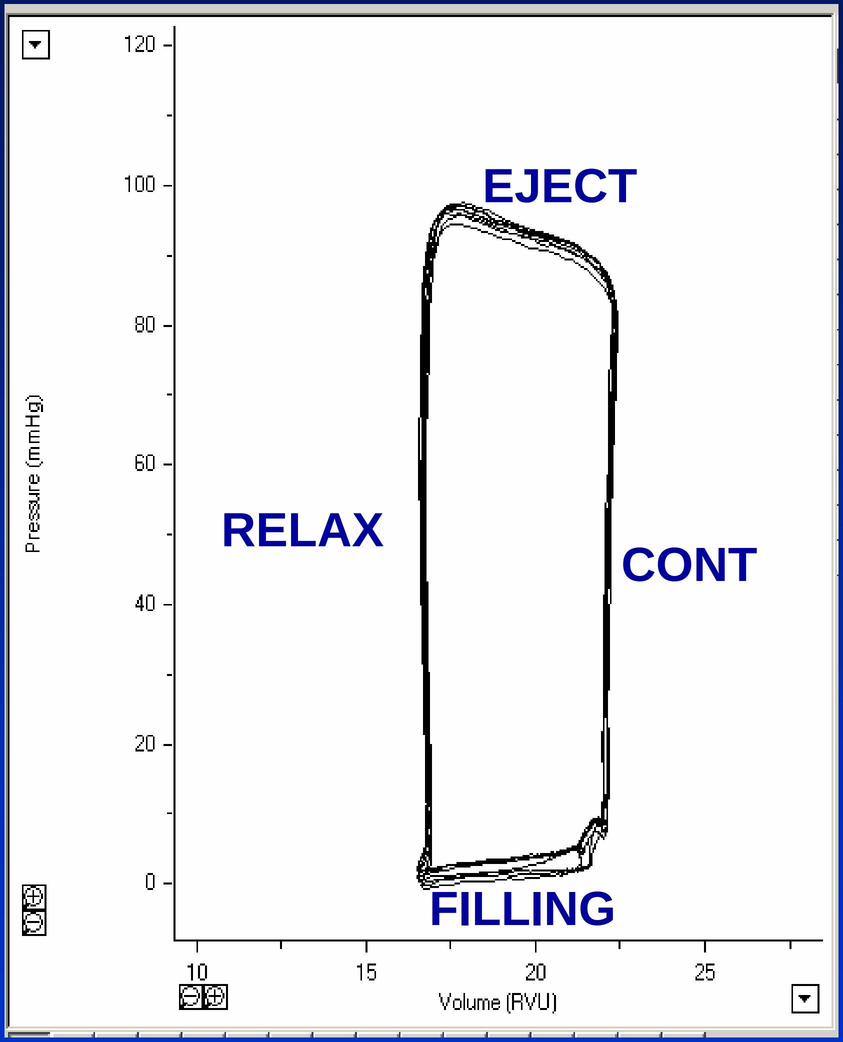


Survival after cardiac arrest

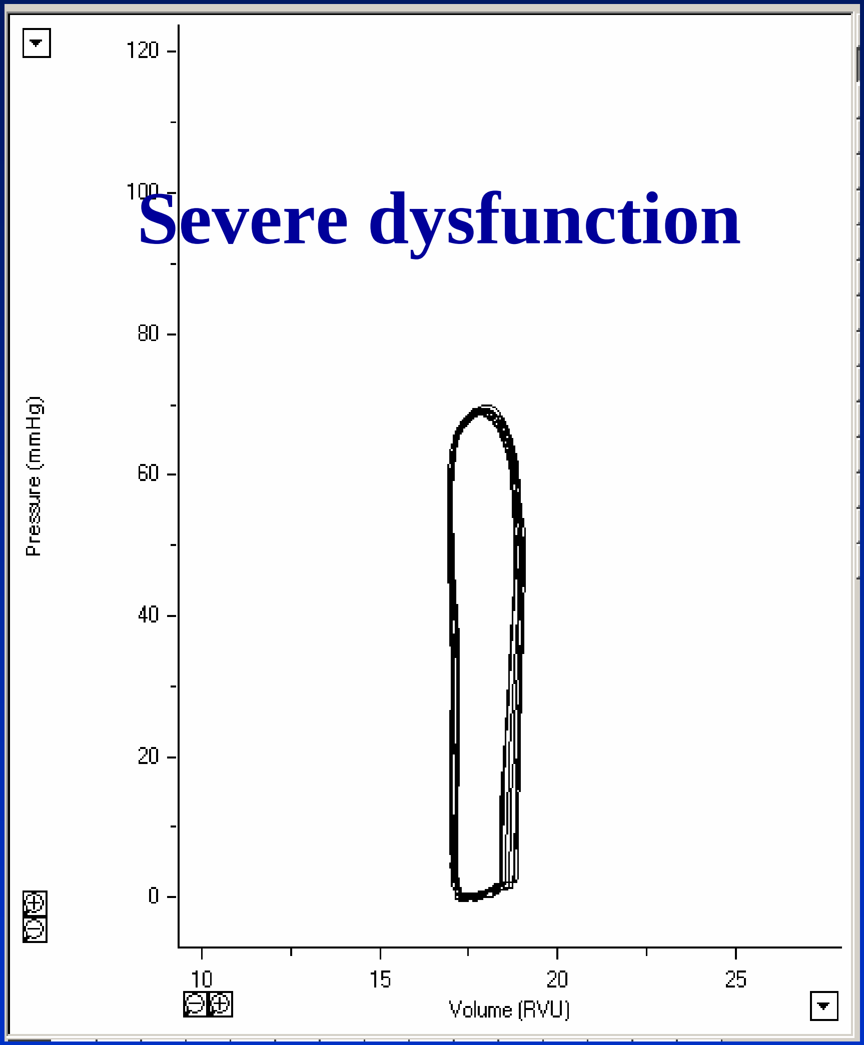


Abella et al. Circulation. 2004;109:2786-2791

A.



B.



Left ventricular pressure-volume loops A. baseline versus B. 2 hr post-resuscitation

Abella et al. Circulation. 2004;109:2786-2791

Timing of Hypothermia during Cardiac Arrest in Mice

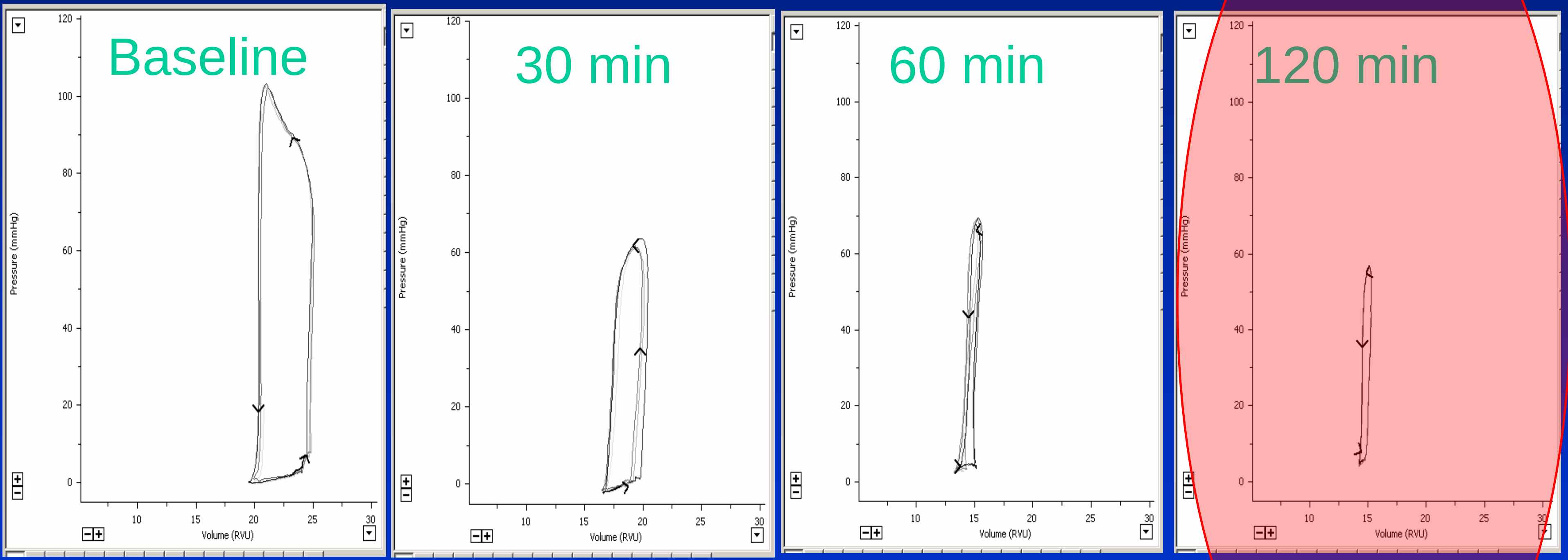
Abella et al. Circulation. 2004;109:2786-2791

	ROSC	6 hours Survival	72 hours Survival
Control	7/10	3/10*	1/10*
Delayed	6/10	1/10*	1/10*
Intra-arr	**9/10**	**7/10**	**6/10**

Abella et al. Circulation. 2004;109:2786-2791

Hypothermia and Heart Function

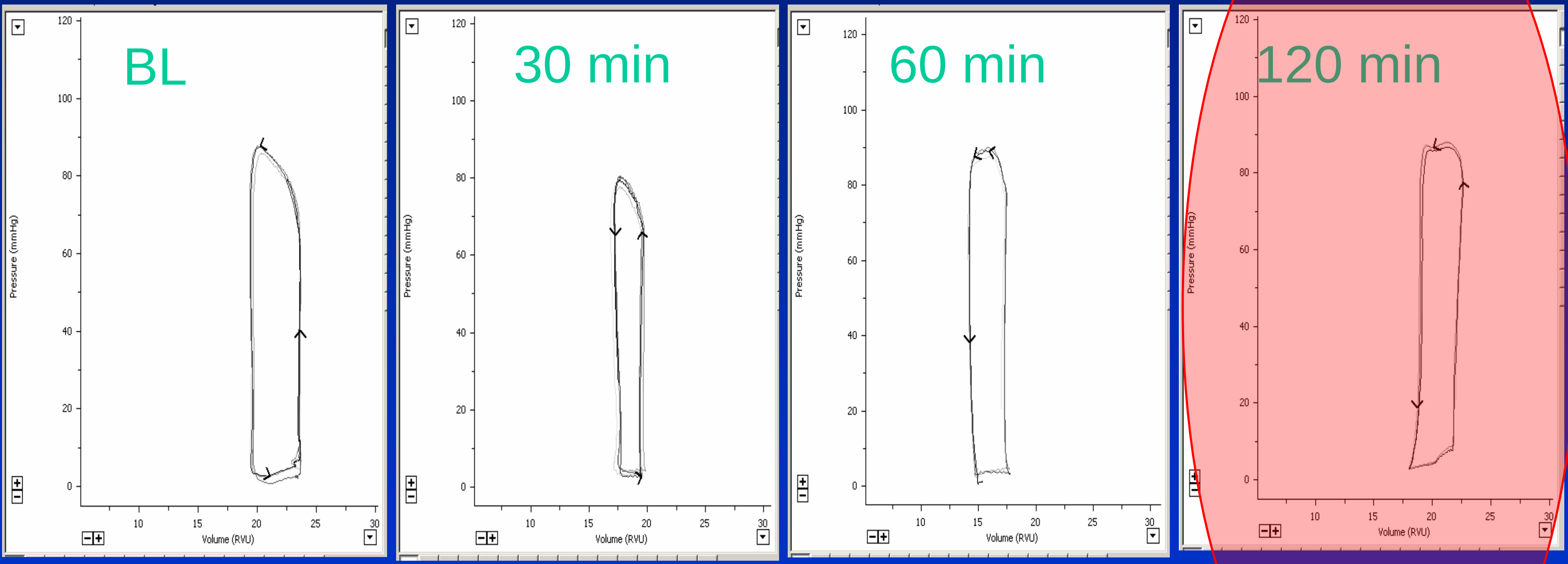
Normothermia:
Pressure-Volume conductance loops



Zhao et al
AHA abstract 2005

Hypothermia and Heart Function

Intra-arrest cooling:
Pressure-Volume conductance loops

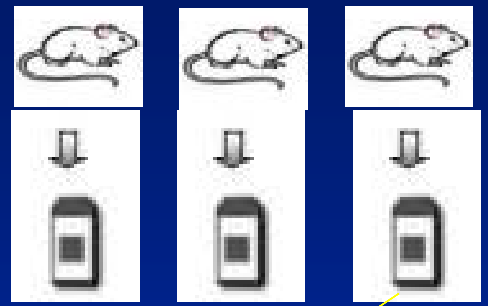


Zhao et al
AHA abstract 2005

Approach (mouse): Gene Array analysis of Heart Stress Responses

Before and After Cardiac Arrest

Sample preparations

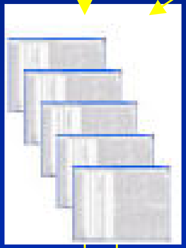


RNA Isolation

Reverse transcription and hybridization

Affymetrix 430 2.0 chips

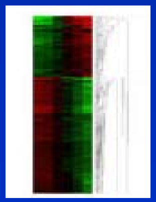
Data preparation



Data filtration,
Data normalization

Project analysis:
Differential expression,
Visualization.

Fold change
quality
ANOVA



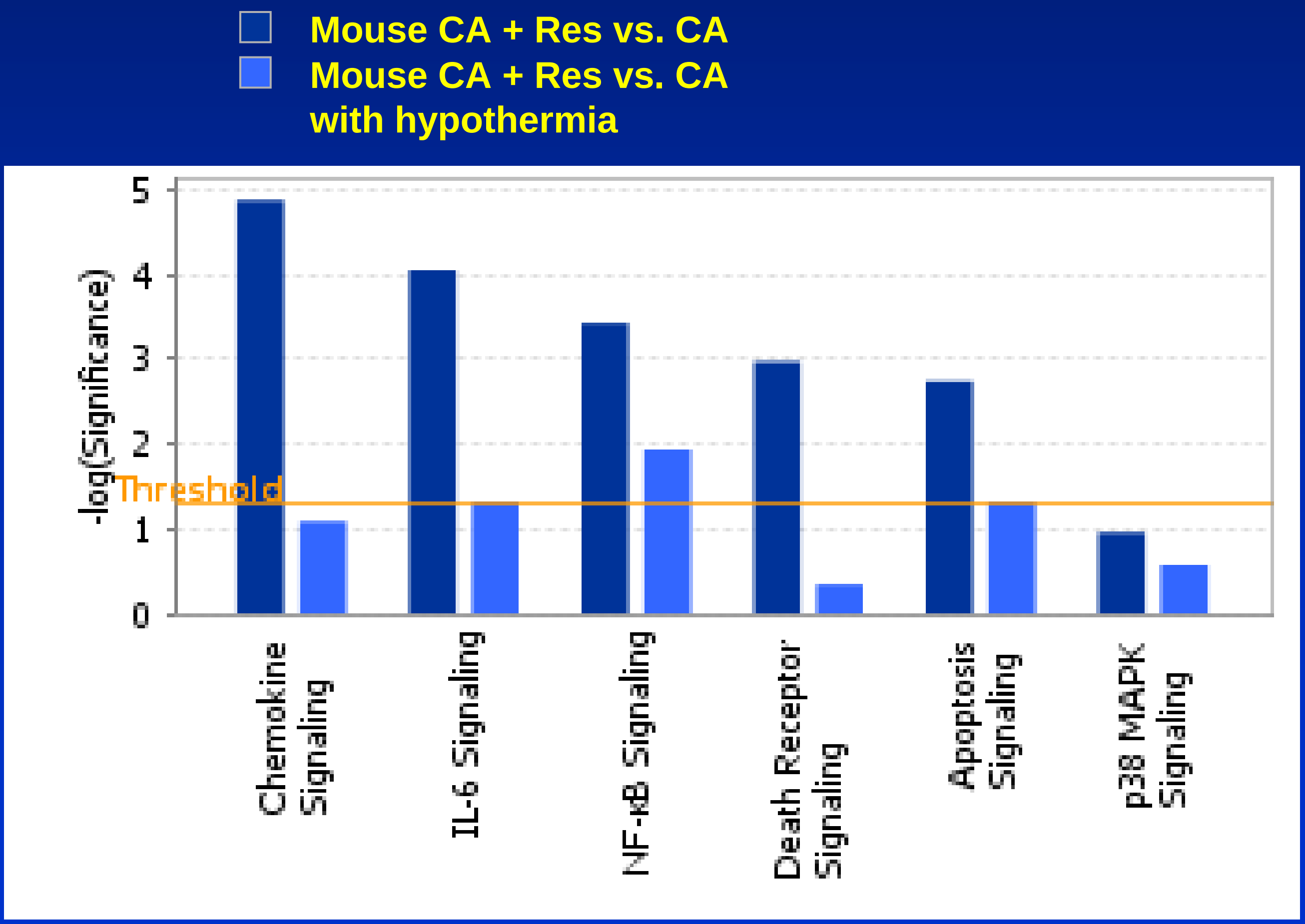
Hierarchical
clustering

Biological Significance

Transcriptional changes at CA and CA/ROSC compared to baseline

Pathway analysis of tissue changes

Hypothermia Attenuates Markers of Immunologic Dysfunction and Death in the Heart



“a Sepsis-like Syndrome”

Adrie, Circulation 2002, 106:562-8

Modeling the Post Cardiac Arrest Syndrome in our Patients:

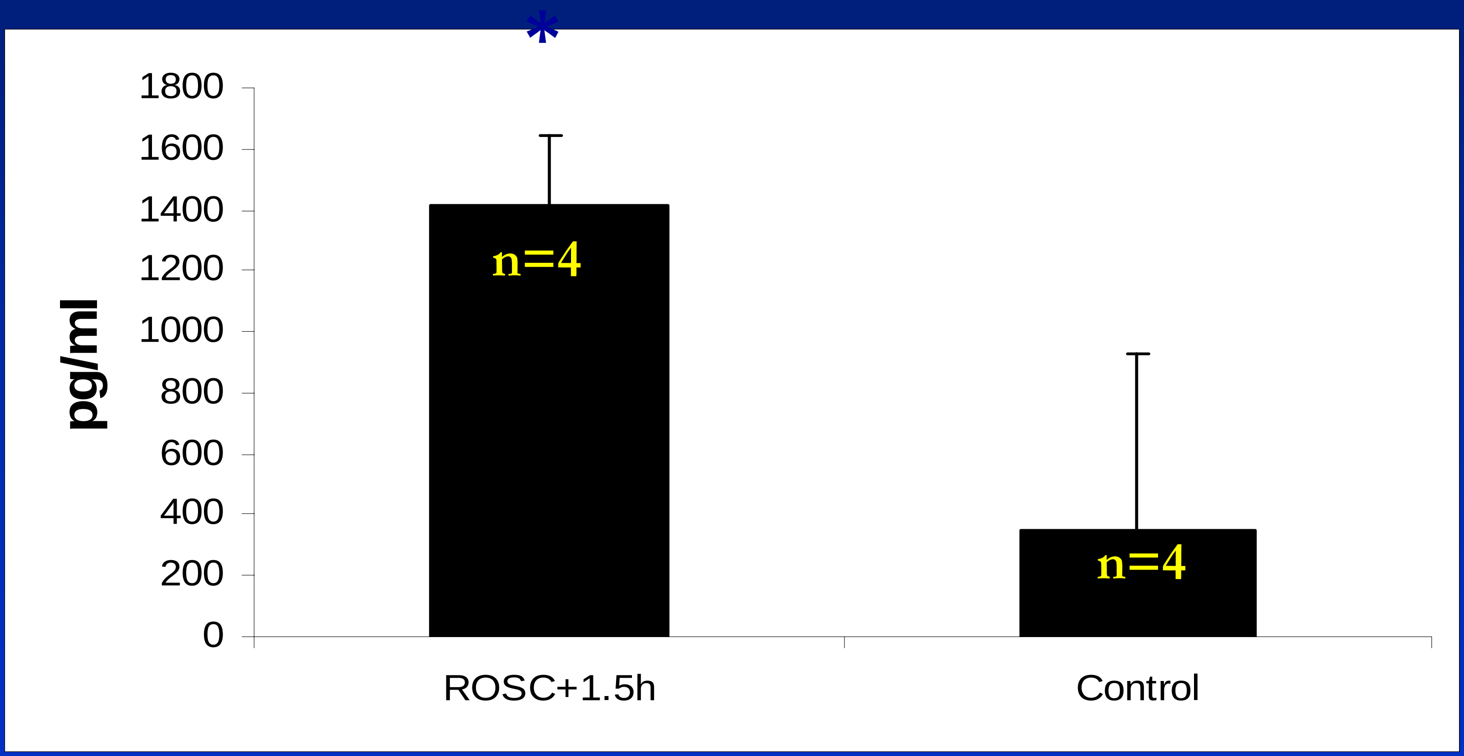
- Hemodynamic instability
  - Myocardial dysfunction
  - Decreased systemic vascular resistance
- Inflammation (systemic inflammatory syndrome, SIRS)
  - ±leukocytosis
  - ± hyperthermia
  - microvascular dysfunction
  - coagulopathy, decreased thrombolysis

SIRS Criteria

T >38ºC or <36ºC
HR >90 bpm
RR >20 bpm
12K < WBC < 4K
(or >10% bands)

Immunologic Dysfunction after Human Cardiac Arrest: the "Cytokine Storm"

Human Plasma IL-6 levels after 1.5 h ROSC



Beiser, unpublished data

A Possible Initiator of Inflammation: Oxidant Stress During CPR and After ROSC

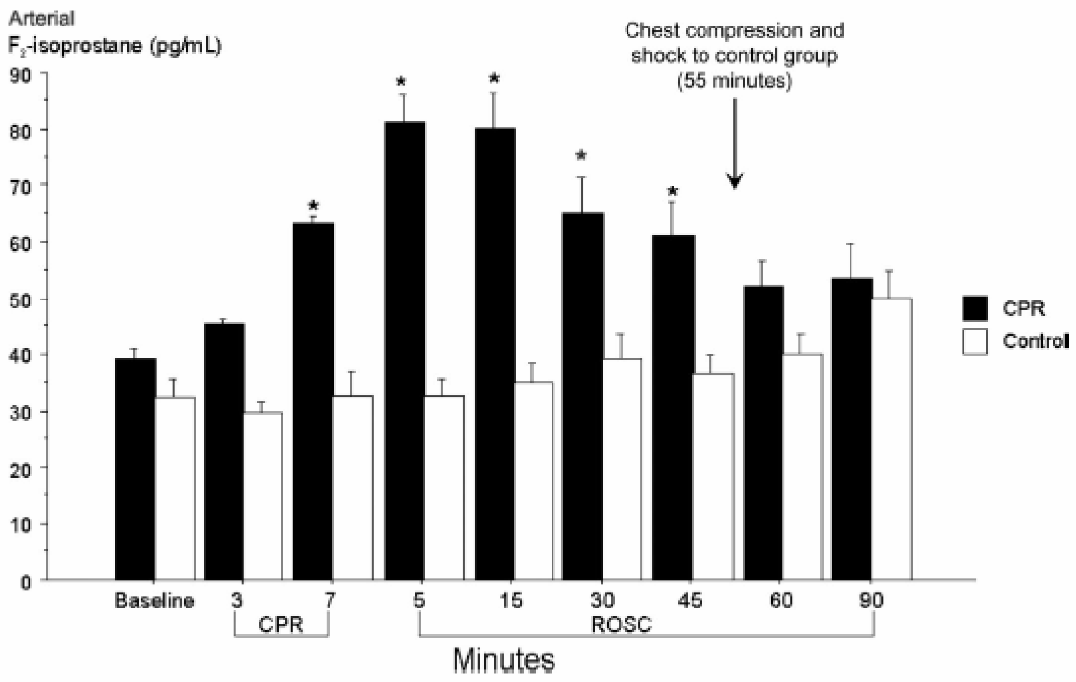
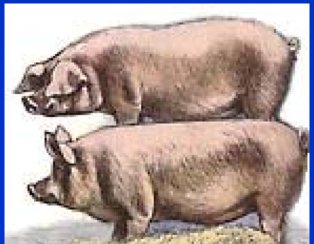


Figure 4. Aortic F_2-isoprostane levels (pg/mL). *CPR*, cardiopulmonary resuscitation; *ROSC*, return of spontaneous circulation. Cardiac arrest group compared with the control group. Mean (±SE), *$p <$ .0006.



Idris. Crit Care Med. 2005;33(9):2043-2048

Role of Mitochondrial Oxidant Generation in Endothelial Cell Responses to Hypoxia

Daryl P. Pearlstein, Mir H. Ali, Paul T. Mungai, Karen L. Hynes,
Bruce L. Gewertz, Paul T. Schumacker

(*Arterioscler Thromb Vasc Biol*. 2002;22:566-573.)

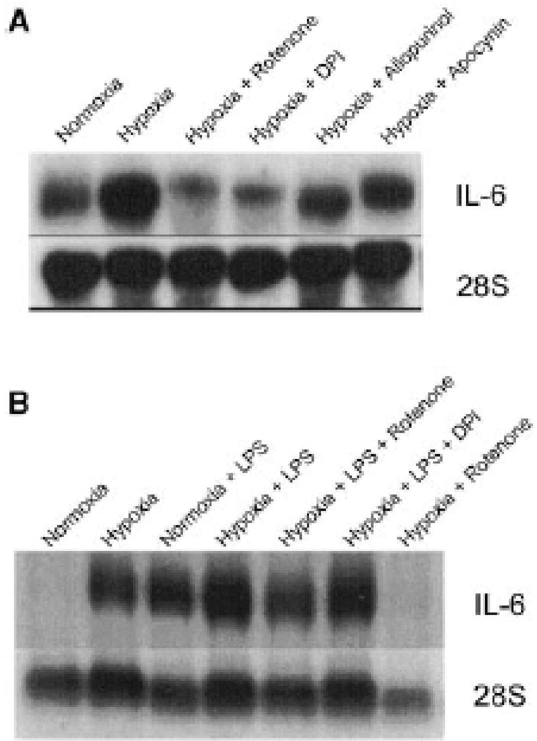
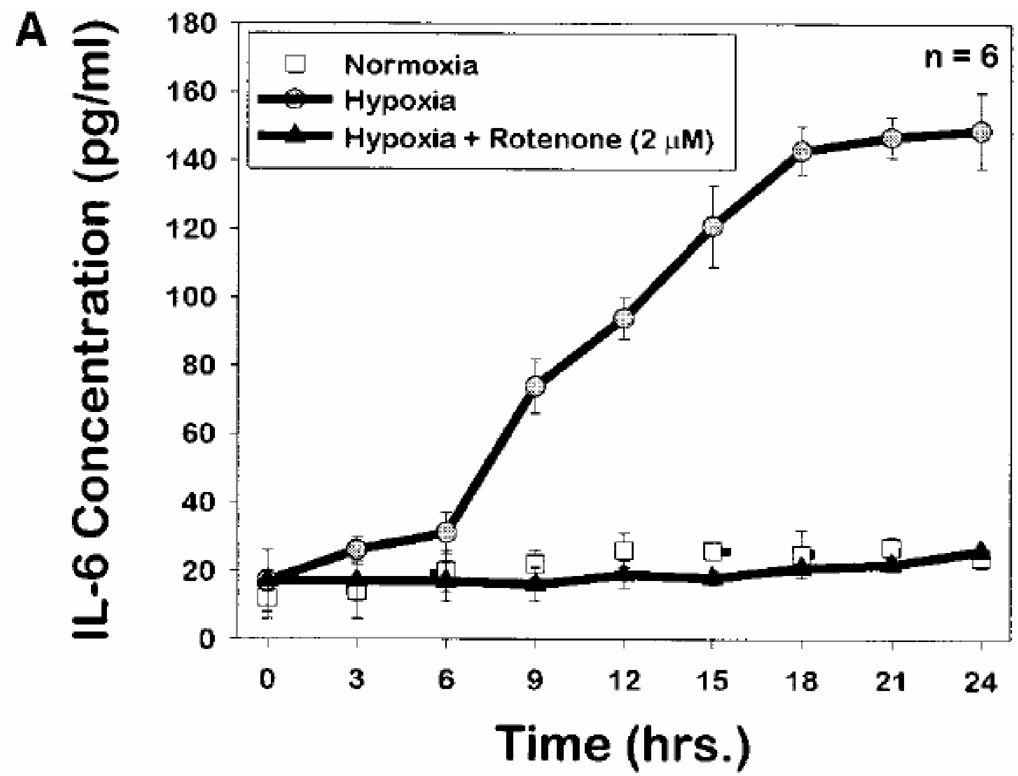
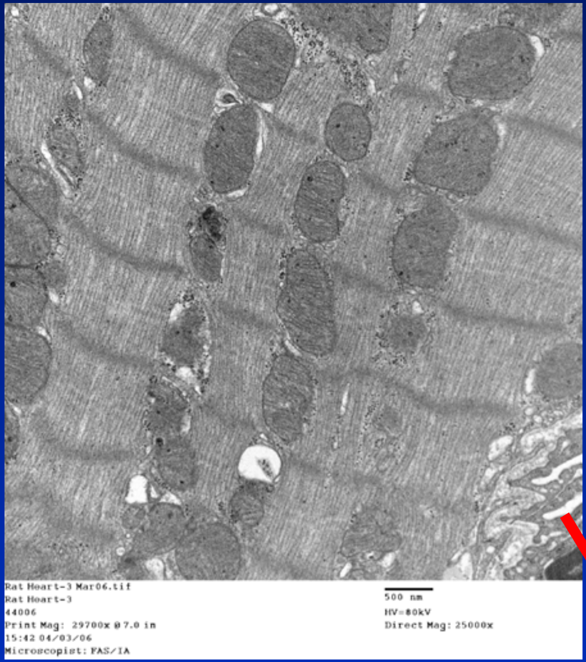


Figure 2. Changes in IL-6 gene expression in response to hypoxia. HUVECs were exposed to hypoxia for 6 hours before RNA collection for analysis of IL-6 message via Northern analysis. a, Effects of inhibitors of ET, NAD(P)H oxidase, and xanthine oxidase. b, Effects of ET inhibitors on the response to LPS.

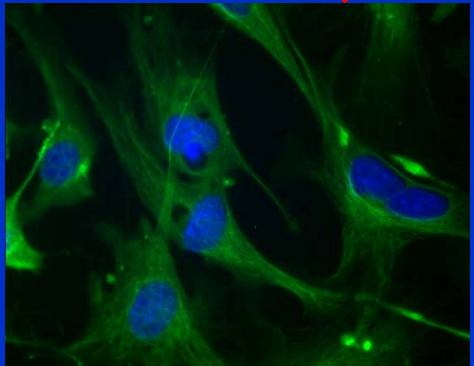


Studying Hypothermia at the Heart Cell Level: Optimal Timing of Cooling?



Heart tissue

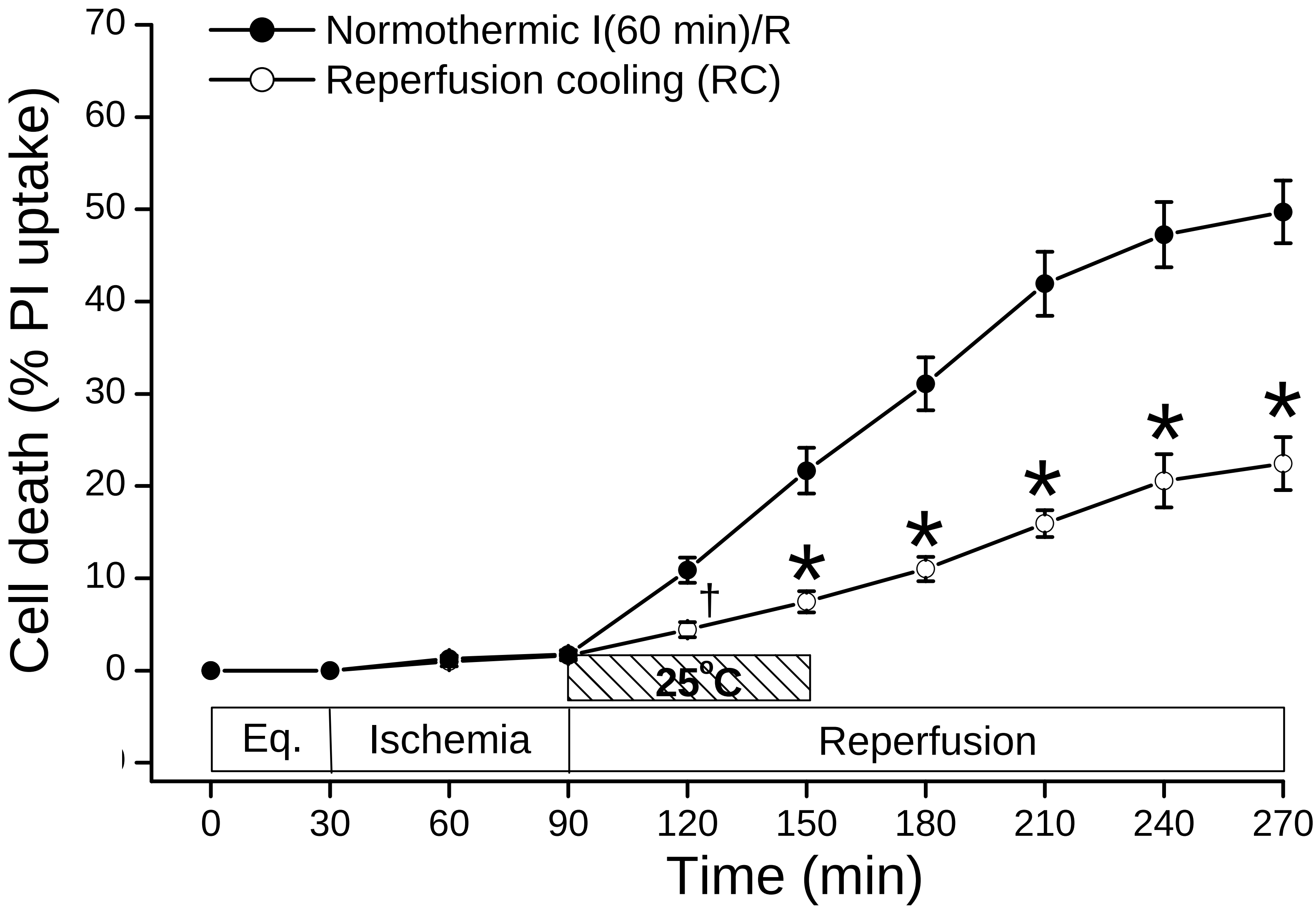
Microscope Perfusion System



Cultured cardiac cells

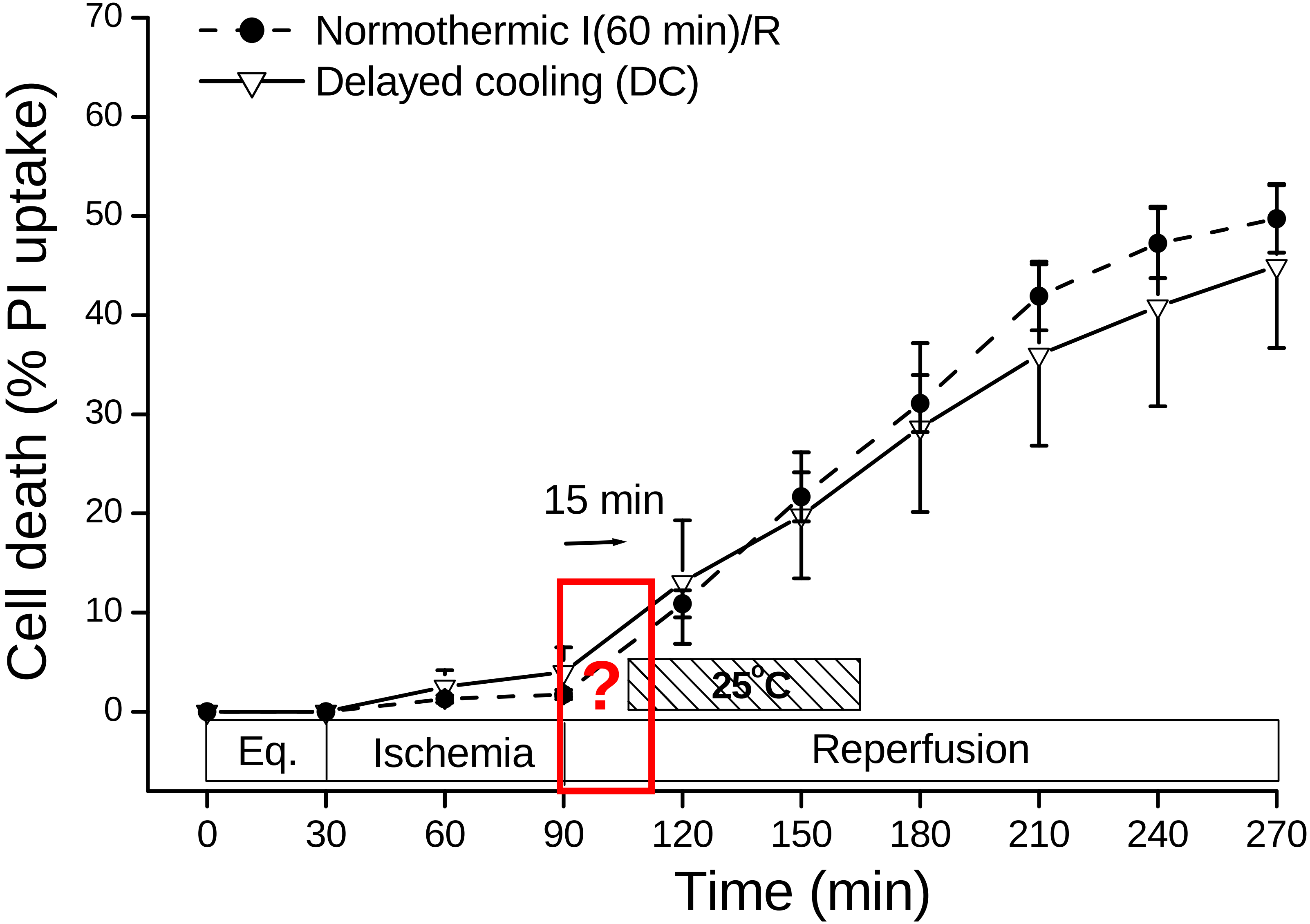
Vanden Hoek et al. Am J Physiol. 1996 Apr;270(4 Pt 2):H1334-41

Chick cardiomyocyte death during I/R and hypothermia



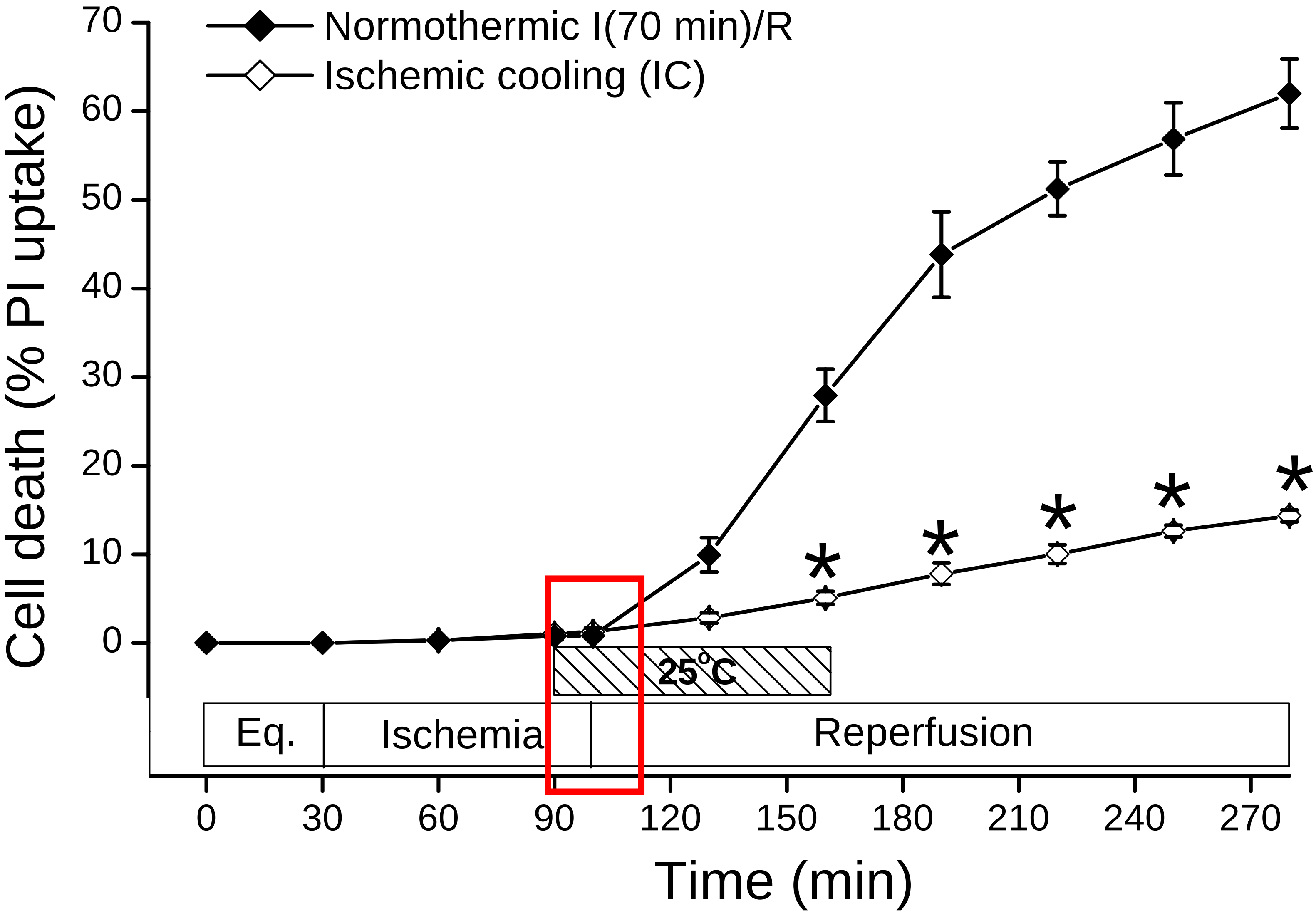
Shao et al. Am J Physiol Heart Circ Physiol. 2007 In press

Delayed cooling abrogates hypothermia protection



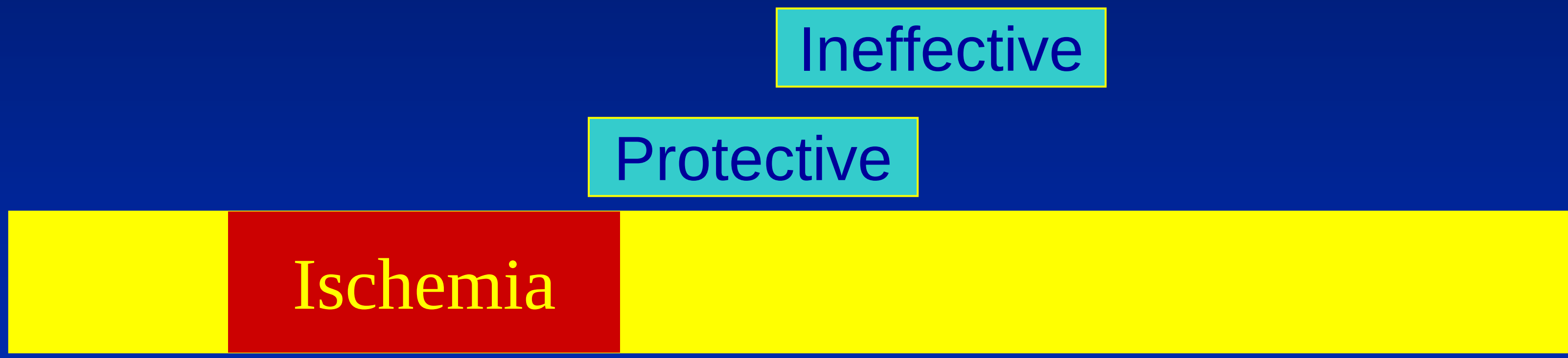
Shao et al. Am J Physiol Heart Circ Physiol. 2007 In press

Intra-ischemia cooling enhances hypothermia protection



Shao et al. Am J Physiol Heart Circ Physiol. 2007 In press

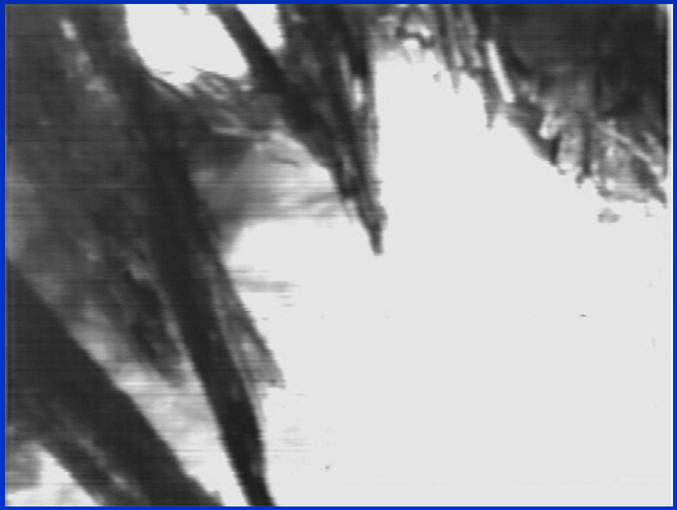
Hypothermia timing and cardiac arrest: if earlier cooling is better, how do we induce intra-ischemic cooling in the clinical setting?



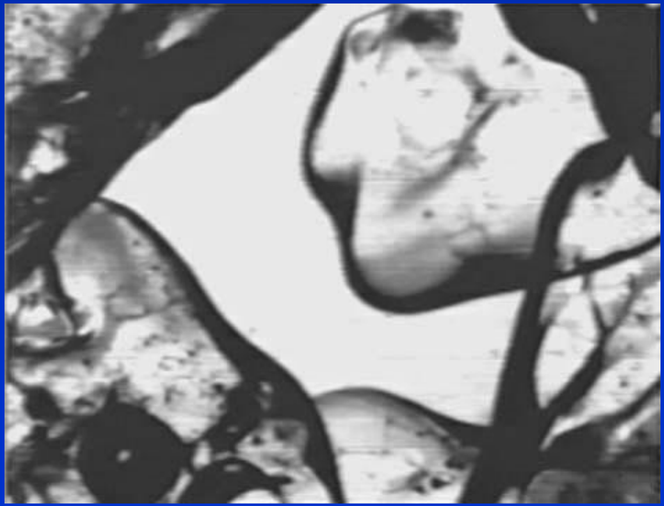
--Cooling in a mouse during CPR is easy.

--Intra-ischemic cooling in patients during CPR is a heat transfer bioengineering challenge!

Micro-particulate
ice slurry
for rapid
cooling



100 um



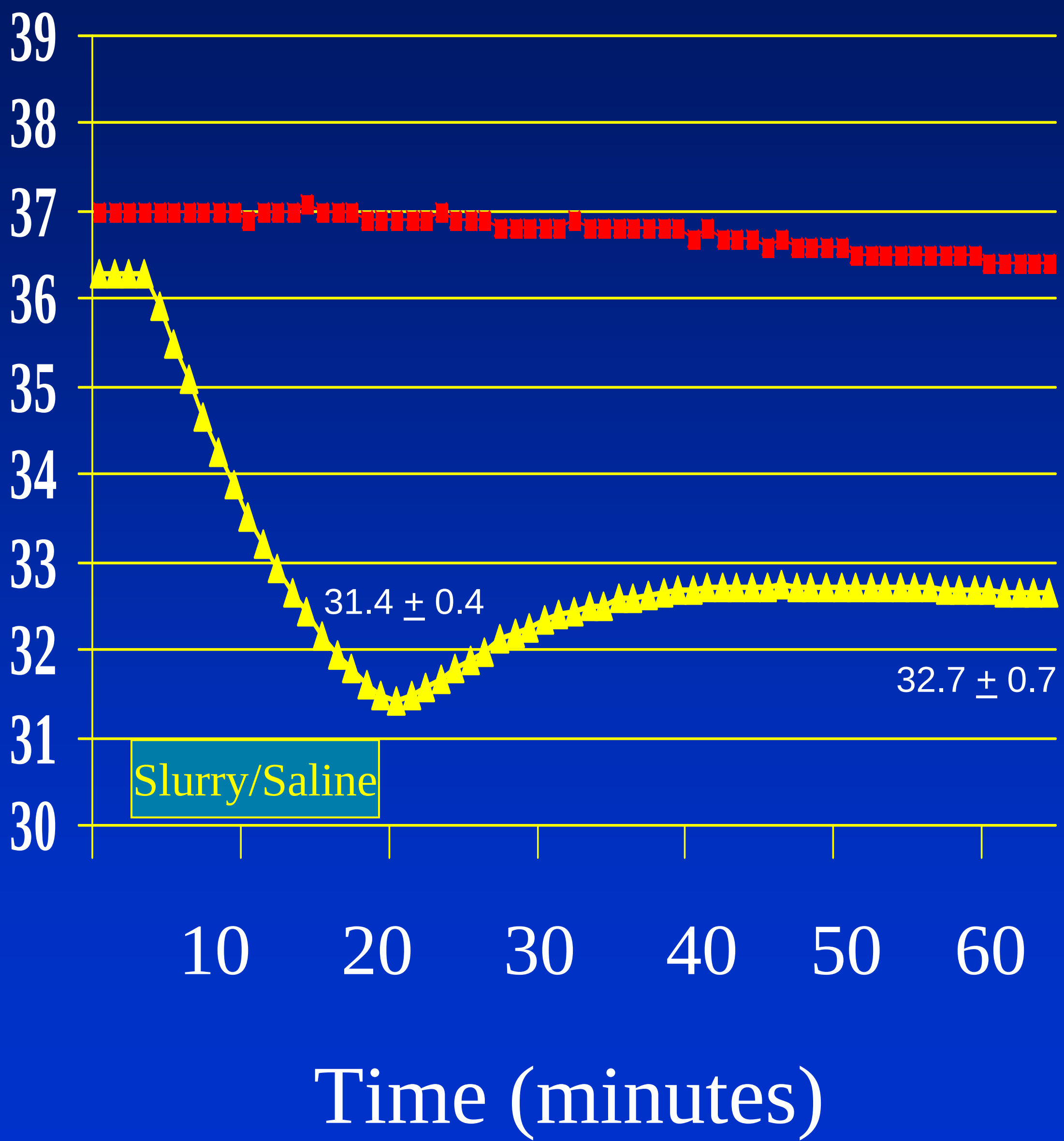
IV slurry in a swine model n=4 each

Total 50 ml/kg
at 120 ml/min

Core brain temp °C

37.5 ± 0.1

36.3 ± 0.8



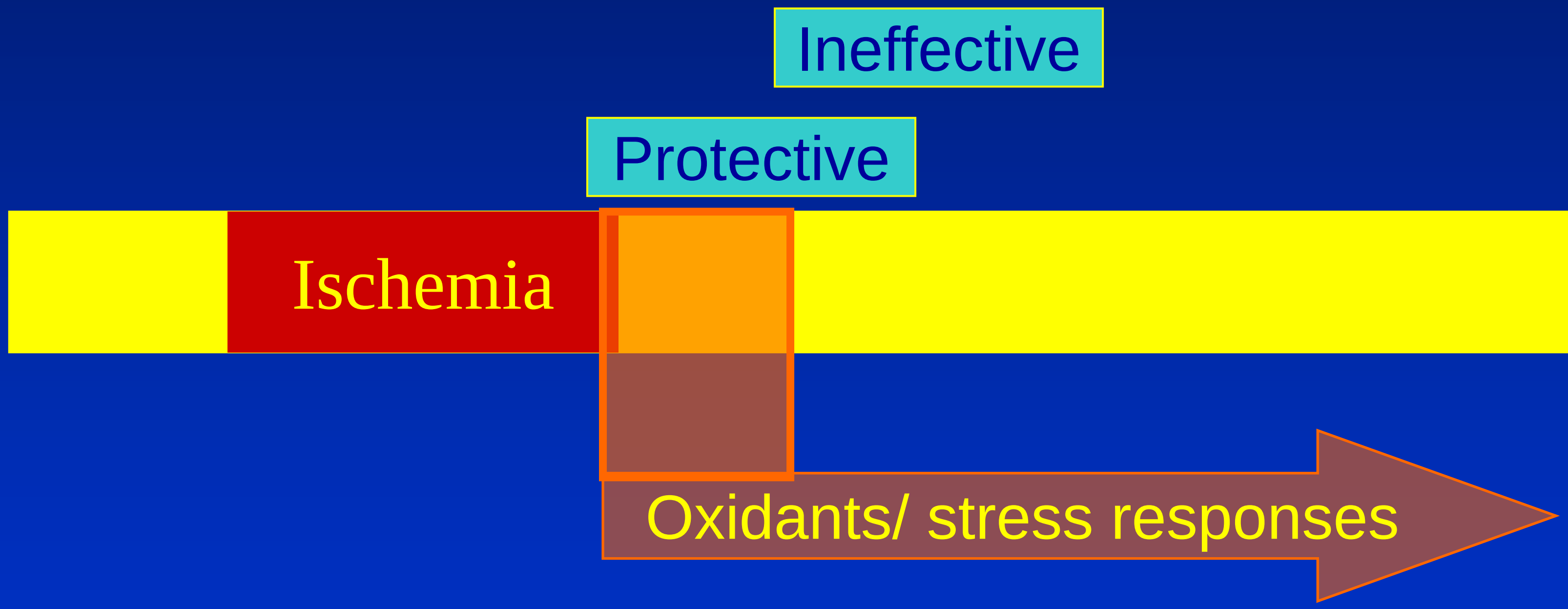
No cooling

Slurry

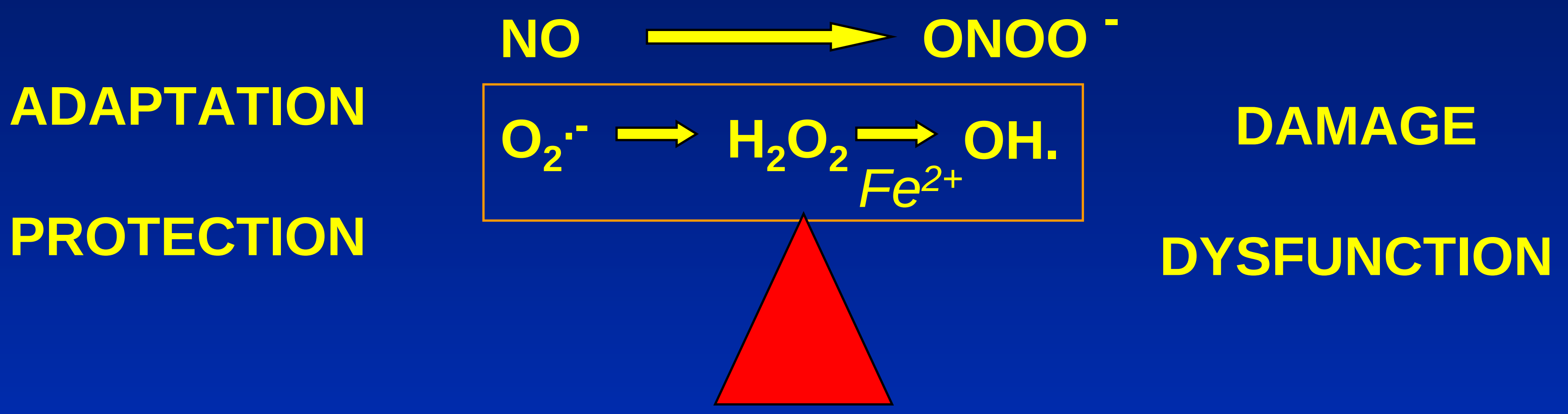
Maximal temp drop:

- 4.9 °C

Hypothermia mechanism of action: how does cooling modulate oxidant stress?



Good and Bad Oxidants: a Critical Balance



Good and Bad Oxidants

ADAPTATION

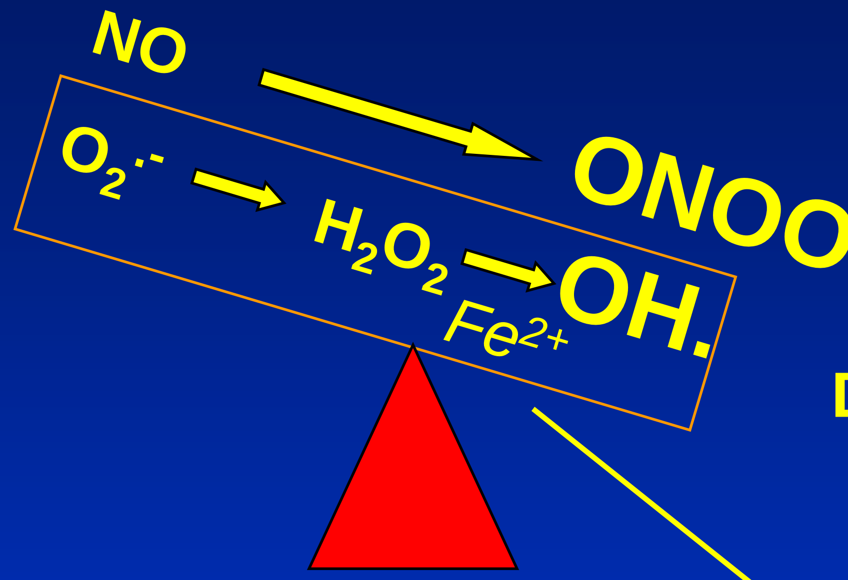
PROTECTION

$NO \rightarrow ONOO^-$

$O_2^{\cdot -} \rightarrow H_2O_2 \xrightarrow{Fe^{2+}} OH^{\cdot}$

Stress

Good and Bad Oxidants

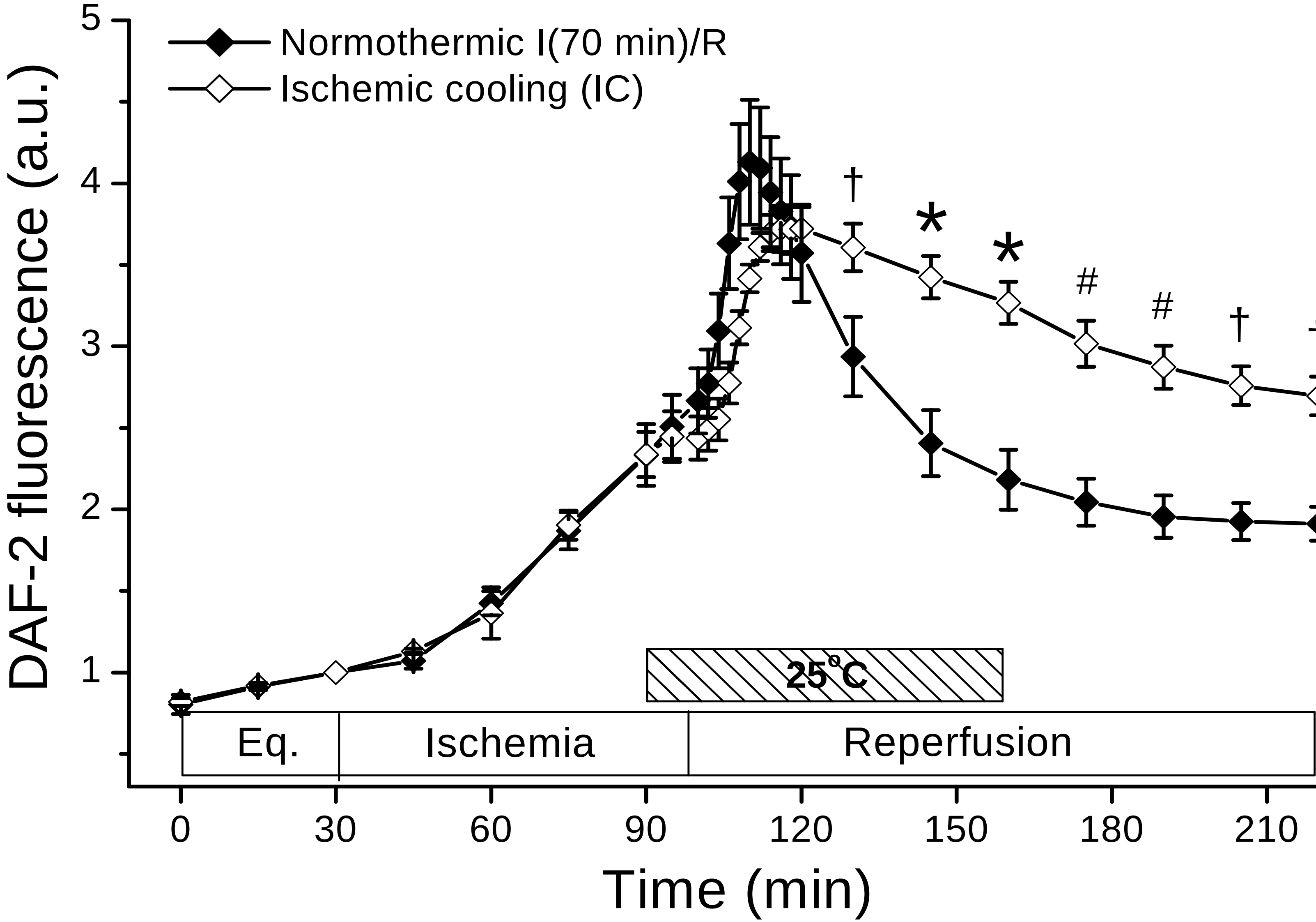


- DAMAGE

DYSFUNCTION

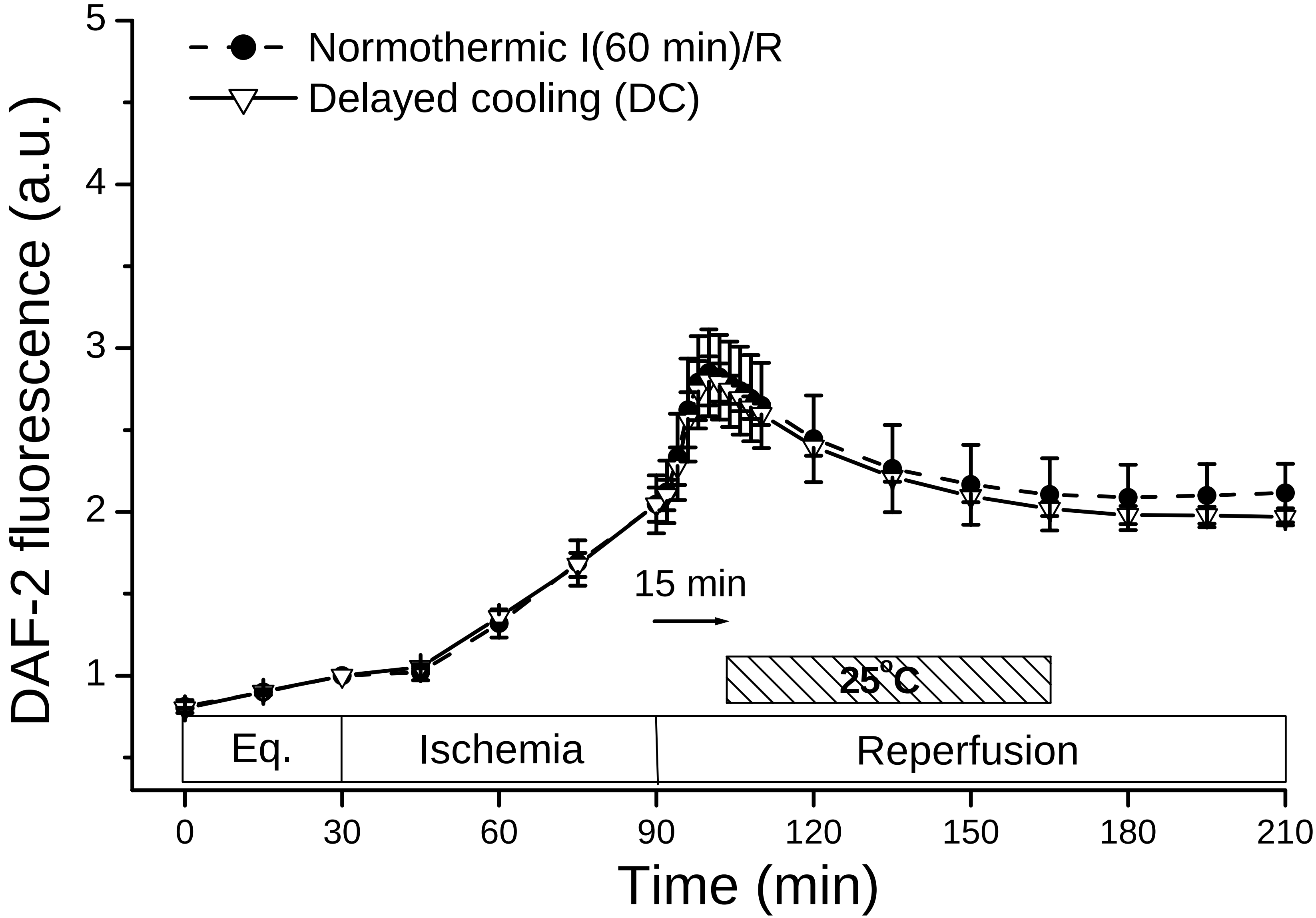
DEATH PATHWAYS

Hypothermia and nitric oxide



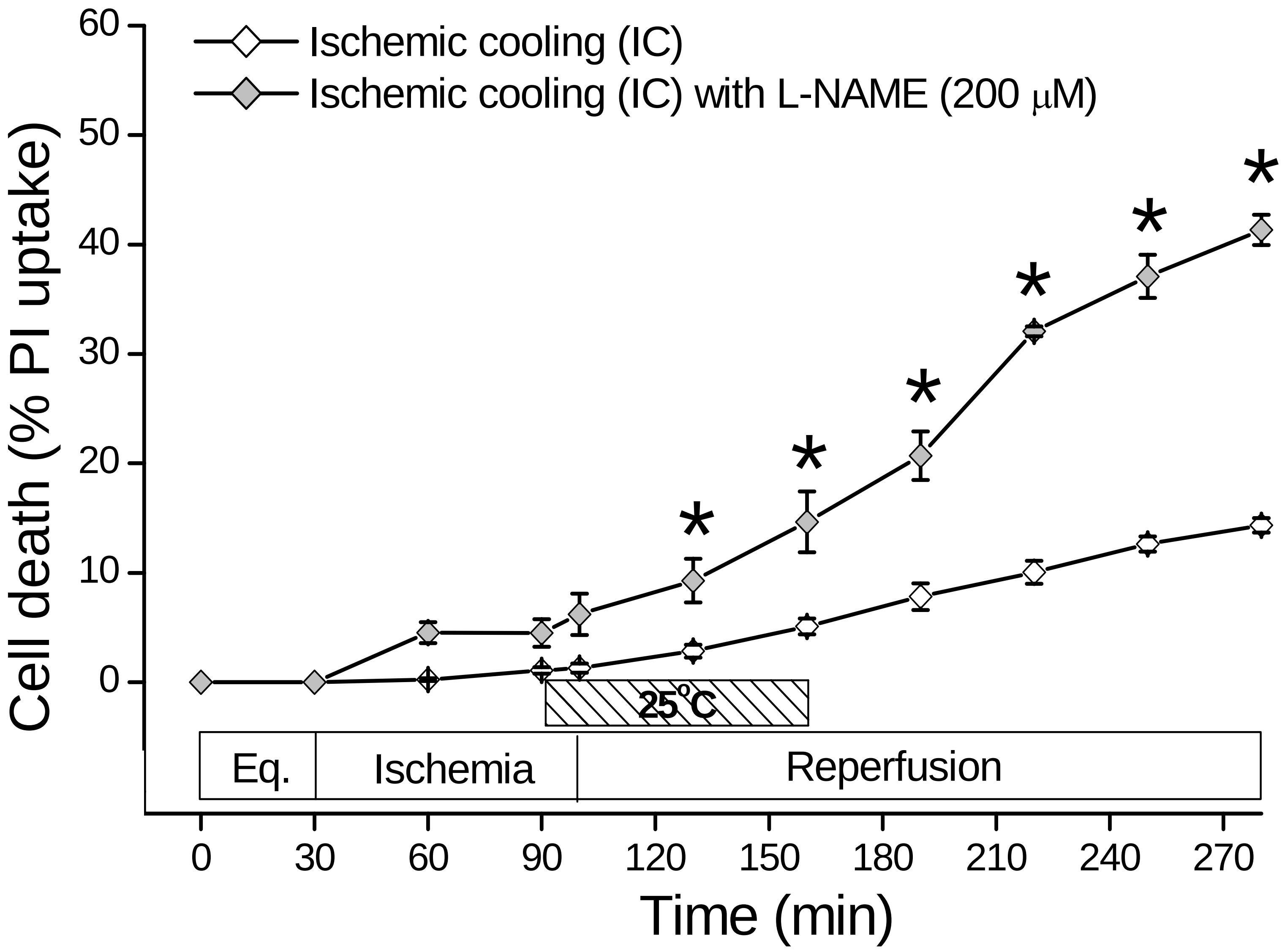
Shao et al. Am J Physiol Heart Circ Physiol. 2007 In press

Hypothermia and nitric oxide



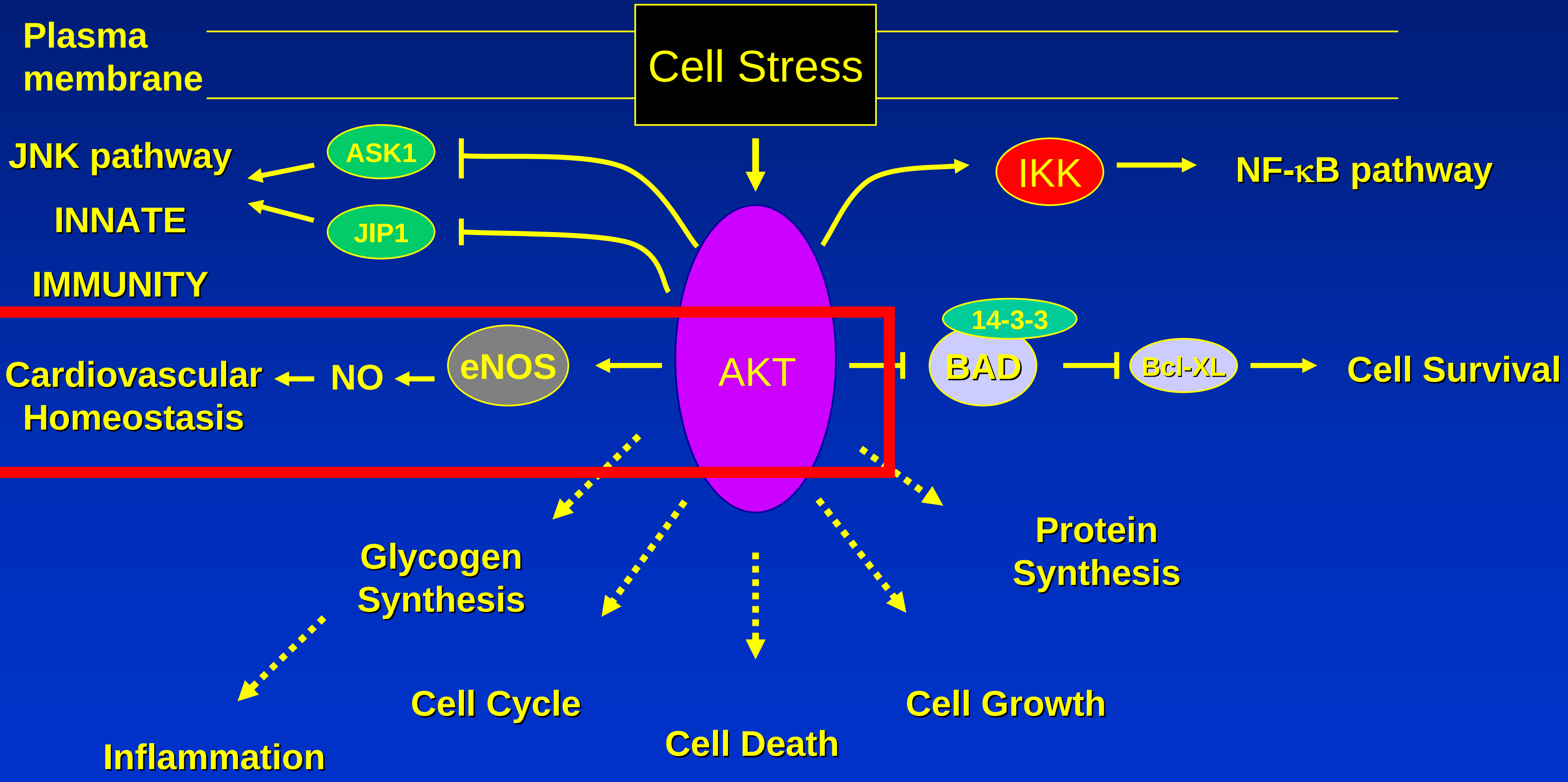
Shao et al. Am J Physiol Heart Circ Physiol. 2007 In press

Hypothermia protection blocked by a NOS inhibitor

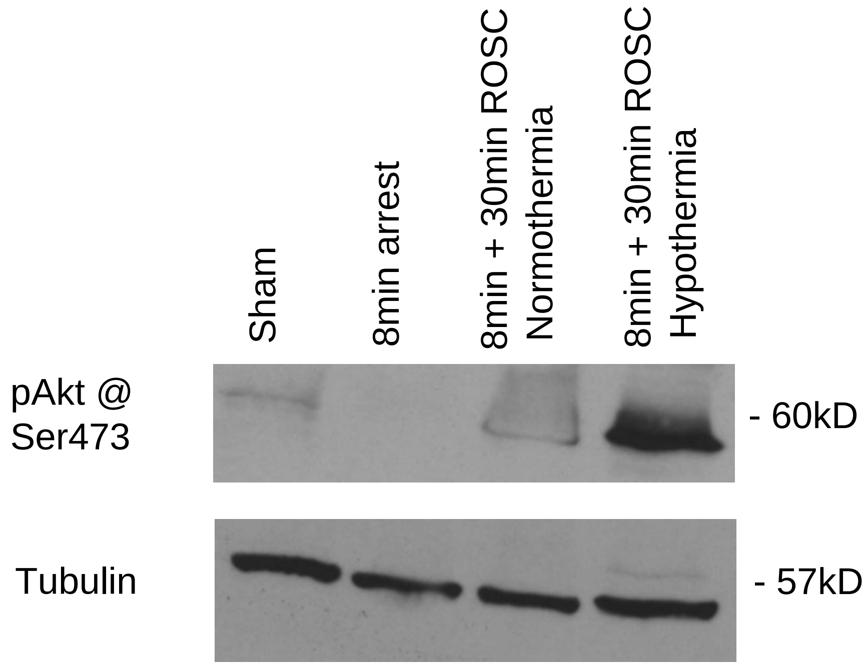


Shao et al. Am J Physiol Heart Circ Physiol. 2007 In press

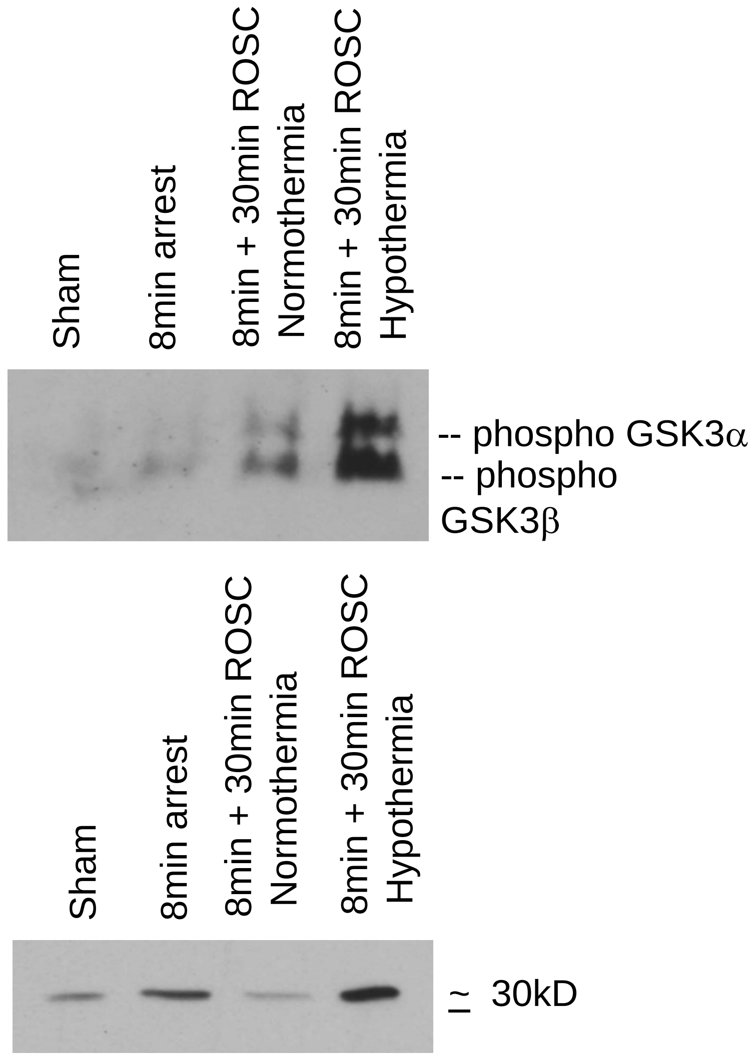
One Critical Regulator of Good/Bad Oxidants: Akt Survival Kinase Signaling Pathway



Therapeutic hypothermia increases heart Akt phosphorylation in murine cardiac arrest



Heart Akt activity is increased by hypothermia in murine cardiac arrest



Sudden death resuscitation

Learning from hypothermia to improve CPR:

--**Akt activation drugs** (e.g. insulin/glucose)

--**Oxidant modulation**, not abrogation!

a) Ventilation gasses that change good/bad oxidant balance quickly

b) Iron chelators to decrease bad oxidants

c) NOS activators plus cofactors (e.g. folate)

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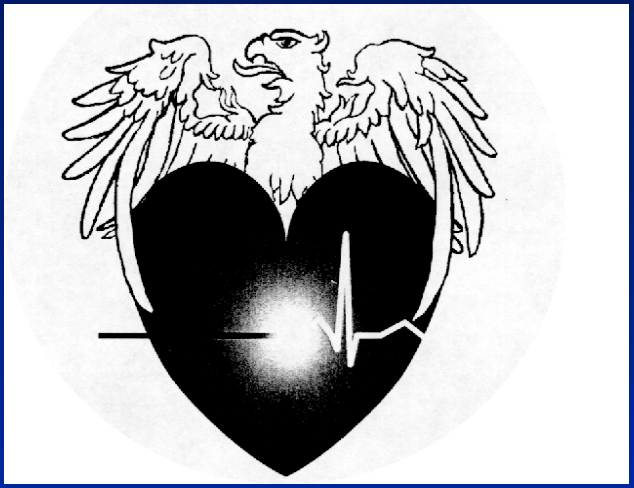

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