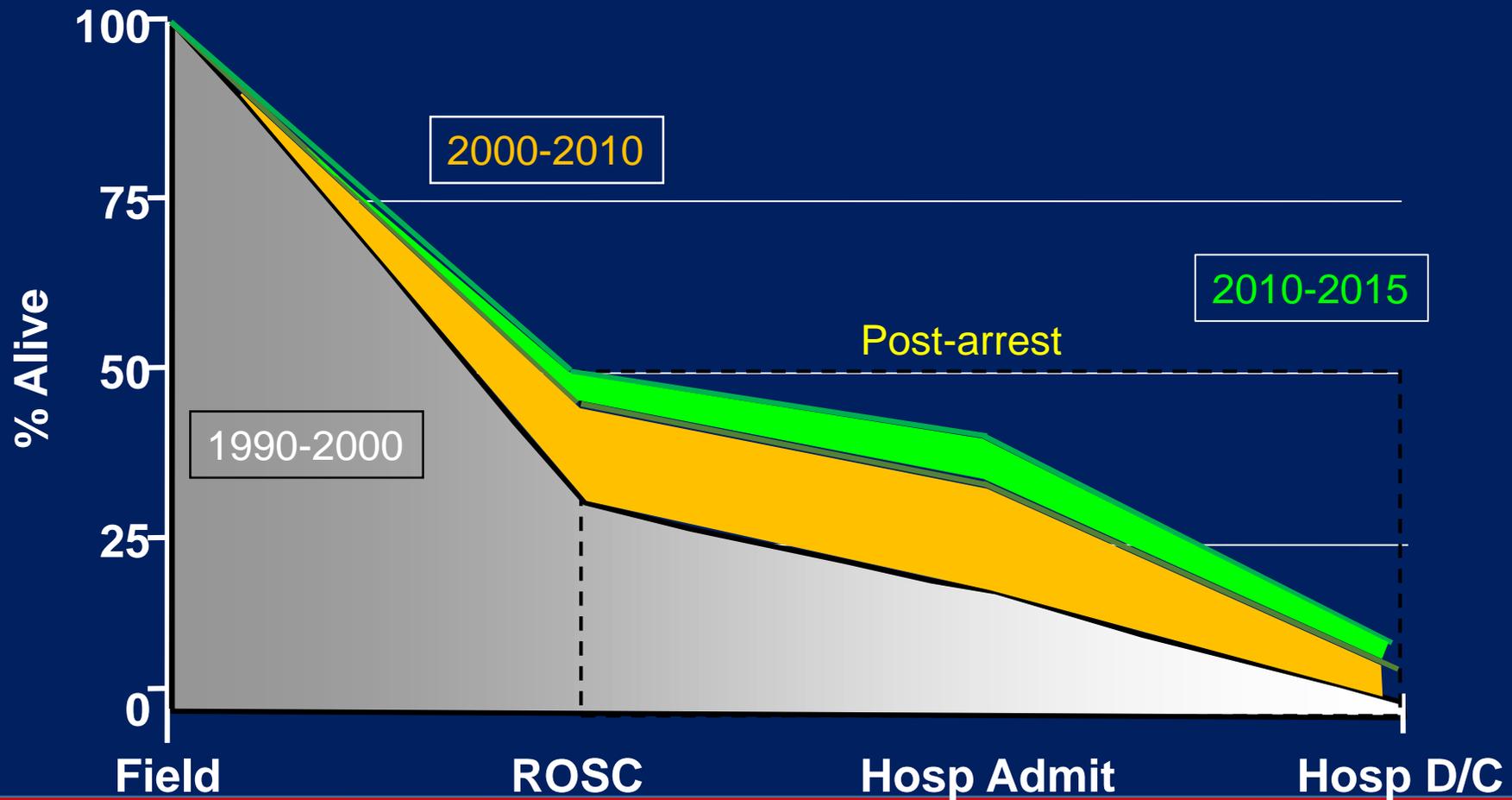


Corso *Post-ROSC*

GIUSEPPE RISTAGNO

Italian Resuscitation Council, Bologna, Italy

Outcome of Cardiac Arrest



ILCOR Consensus Statement

Post-Cardiac Arrest Syndrome

Epidemiology, Pathophysiology, Treatment, and Prognostication

A Consensus Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council

Endorsed by the American College of Emergency Physicians, Society for Academic Emergency Medicine, Society of Critical Care Medicine, and Neurocritical Care Society

Robert W. Neumar, MD, PhD, Co-Chair; Jerry P. Nolan, FRCA, FCEM, Co-Chair; Christophe Adrie, MD, PhD; Mayuki Aibiki, MD, PhD; Robert A. Berg, MD, FAHA; Bernd W. Böttiger, MD, DEAA; Clifton Callaway, MD, PhD; Robert S.B. Clark, MD; Romergryko G. Geocadin, MD; Edward C. Jauch, MD, MS; Karl B. Kern, MD; Ivan Laurent, MD; W.T. Longstreth, Jr, MD, MPH; Raina M. Merchant, MD; Peter Morley, MBBS, FRACP, FANZCA, FJFICM; Laurie J. Morrison, MD, MSc; Vinay Nadkarni, MD, FAHA; Mary Ann Peberdy, MD, FAHA; Emanuel P. Rivers, MD, MPH; Antonio Rodriguez-Nunez, MD, PhD; Frank W. Sellke, MD; Christian Spaulding, MD; Kjetil Sunde, MD, PhD; Terry Vanden Hoek, MD

Progettazione oggetti formativi

Corso Post-ROSC 1° Livello

Workshop Post-ROSC 2° Livello Adulto

Obiettivi generali → saper:

- **identificare pz da sottoporre al protocollo post rosc**
- **le manovre necessarie per la stabilizzazione**
- **indagare la causa dell'AC e correggerla (identificare SCA)**
- **massimizzare la protezione d'organo con particolare attenzione al SNC (è possibile la perdita dell'autoregolazione flusso cerebrale)**
- **ottimizzare il supporto d'organo (emodinamica e ventilazione, metabolica)**
- **come gestire la temperatura**
- **valutare oggettivamente la prognosi**

Workshop Post-ROSC 2° Livello Adulto

Obiettivi: Gestione completa del paziente adulto post arresto in ambiente intensivo (paziente comatoso)

Destinatari: Operatori sanitari (medici e infermieri) esperti di rianimazione, terapia intensiva cardiologica, semi-intensiva

Struttura: Lezioni frontali, update, discussione casi clinici, meet the expert, take home message

Durata: 1 giorno (programmazione 2 corsi/anno e/o come eventi pre-congressuali)

Facilitatori: esperti intensivi + 1 facilitatore esperto

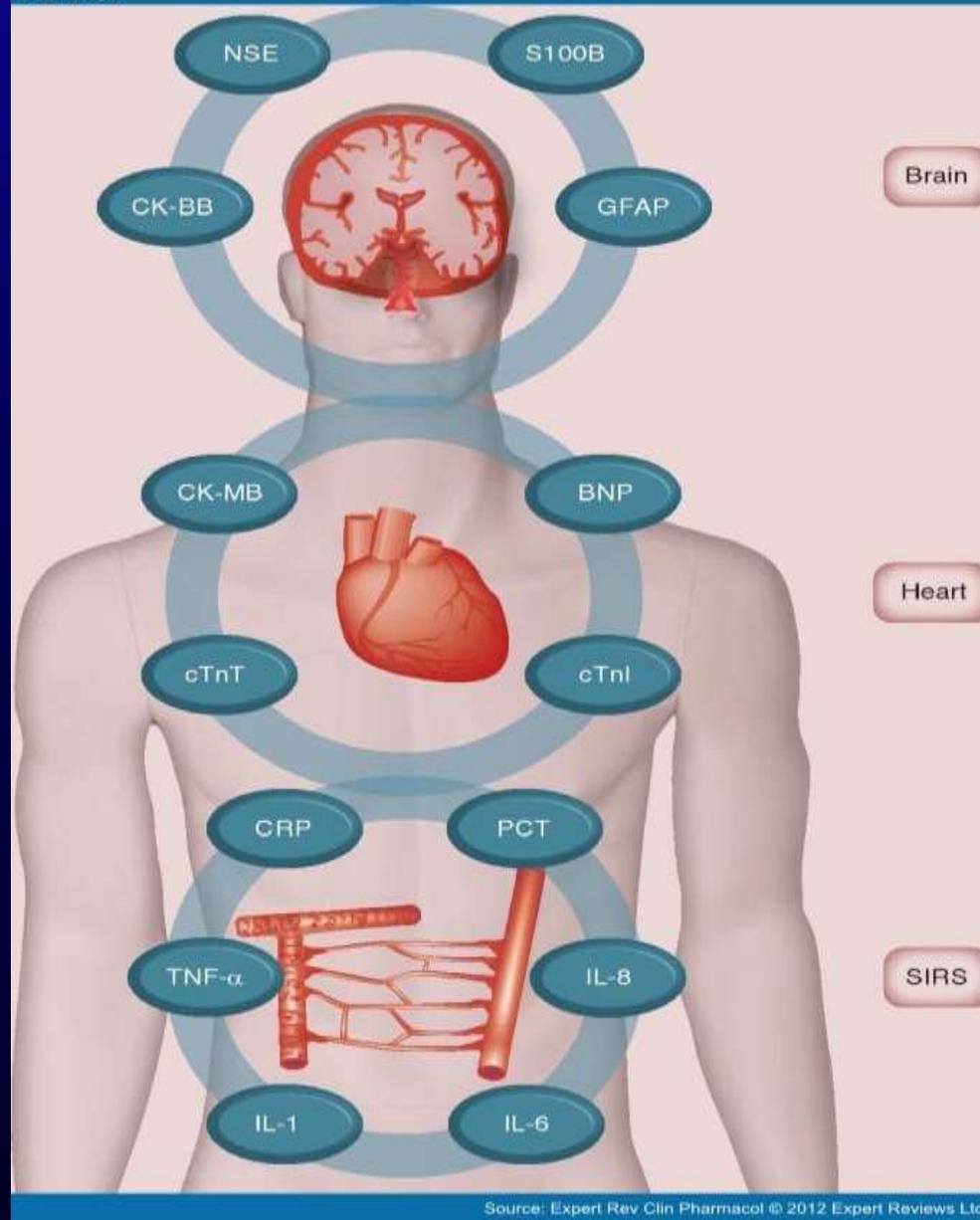
Requisiti per accedere: Consigliato ALS, gestire almeno 10-20 casi/anno

Valutazione: pre-test / post-test (valutazione approccio PBL)

Materiale Didattico: Manuale Post-ROSC consigliato + parte Web con reference aggiornate

Argomenti da trattare approfonditamente durante corso 2° livello:

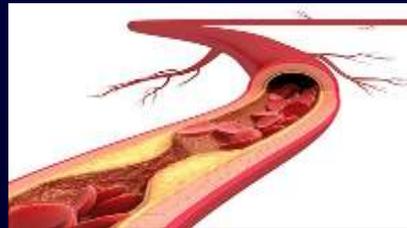
- Fisiopatologia
- Danno d'organo
- Riperfusione
- Percorso diagnostico terapeutico
- Gestione emodinamica (amine, vasopressori, funzione cardio)
- Gestione ventilatoria
- Gestione della temperatura
- Gestione glicemia metabolismo
- EEG e Prognostication
- Supporto fine vita e donazione d'organo



“Post – Resuscitation Period”



Myocardial Dysfunction
Neurological Dysfunction
Systemic Reperfusion



Negovsky VA. Resuscitation 1972 Brown CG, et al. N Engl J Med 1986
Adrie C, et al. Curr Opin Crit Care 2004 Nolan J, et al. Resuscitation 2008
ERC guidelines 2010

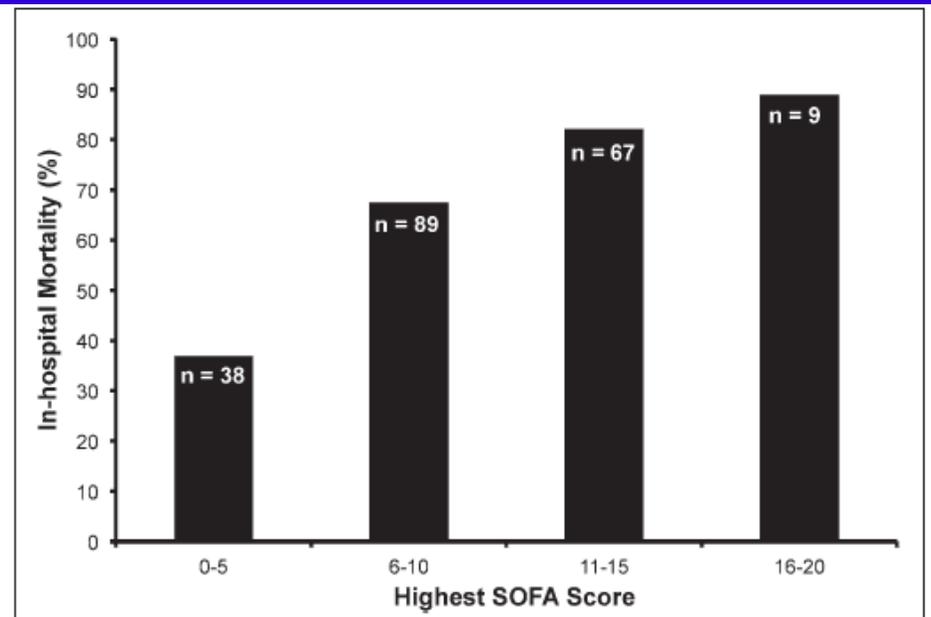
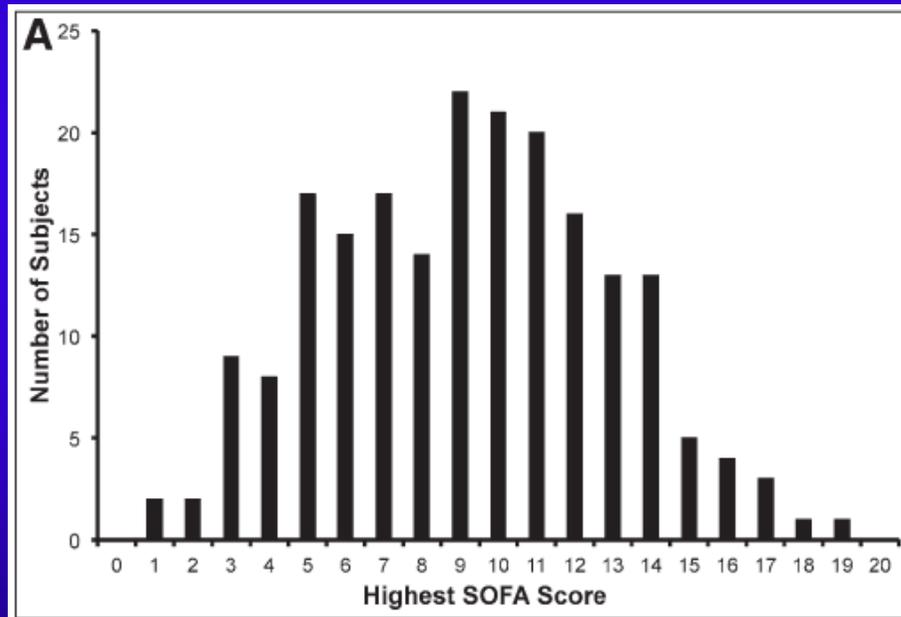
Multiple Organ Dysfunction After Return of Spontaneous Circulation in Postcardiac Arrest Syndrome

Crit Care Med 2013

Brian W. Roberts, MD¹; J. Hope Kilgannon, MD¹; Michael E. Chansky, MD¹; Neil Mittal, MD¹; Jonathan Wooden, MD¹; Joseph E. Parrillo, MD²; Stephen Trzeciak, MD, MPH^{1,2}

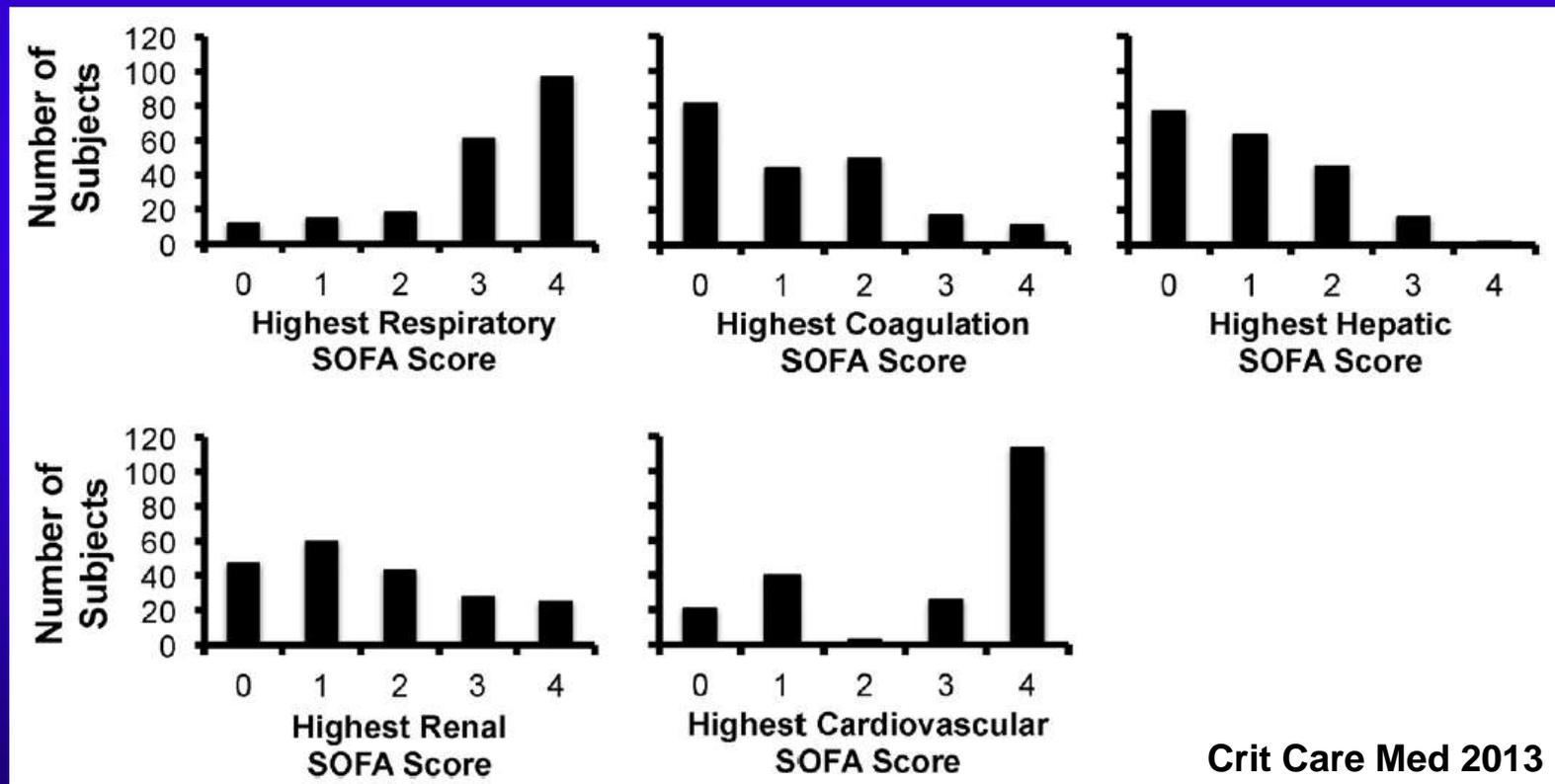
203 pts: 96% some degree of extra cerebral organ dysfunction

66% severe dysfunction in 1 or 2 extra cerebral organs (cardiovascular/respiratory)



Highest extracerebral SOFA → independent predictor of in-hospital mortality:
OR 1.95 [1.15-3.29]

Component	All Subjects	Survivors	Nonsurvivors
Respiratory	3 (3-4)	3 (2-3)	4 (3-4)
Coagulation	1 (0-2)	1 (0-2)	1 (0-2)
Hepatic	1 (0-2)	1 (0-2)	1 (0-2)
Renal	1 (1-3)	1 (0-2)	1 (1-3)
Cardiovascular	4 (1-4)	1 (1-4)	4 (3-4)



Cardiac arrest: a sepsis like syndrome

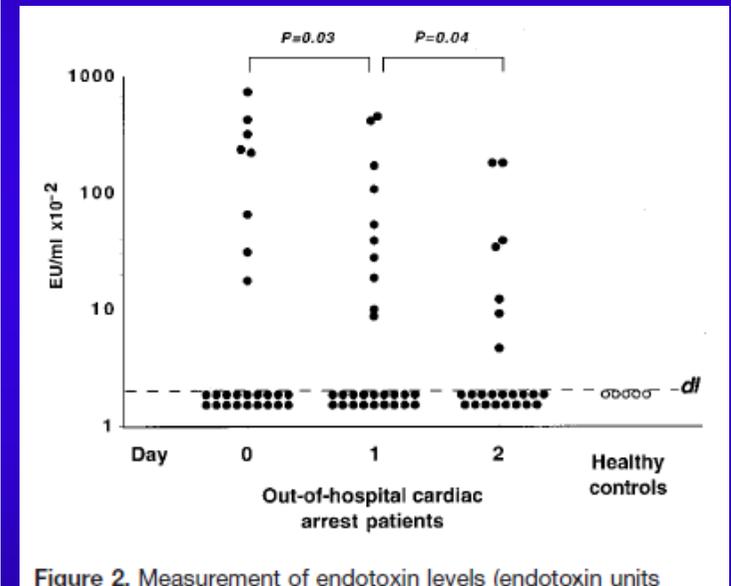
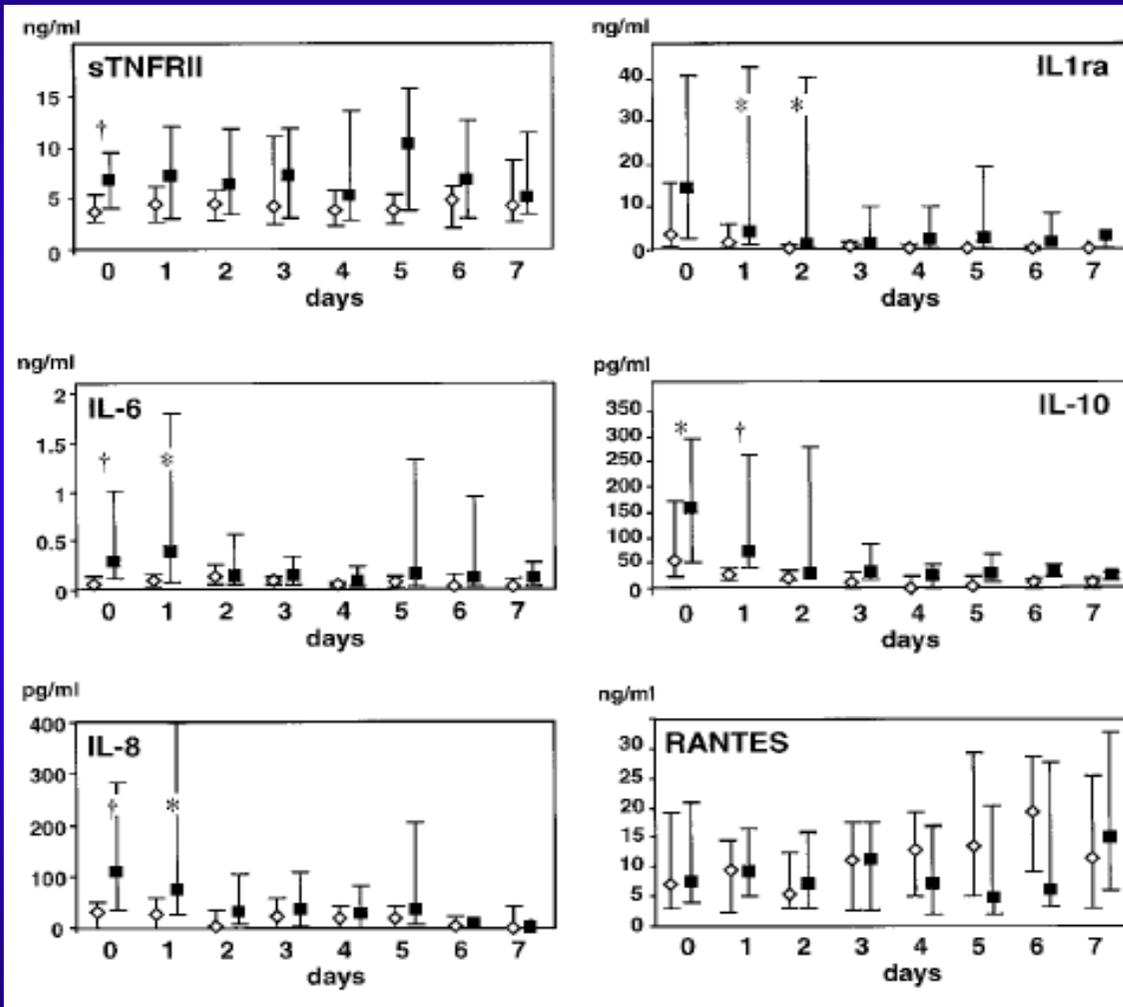
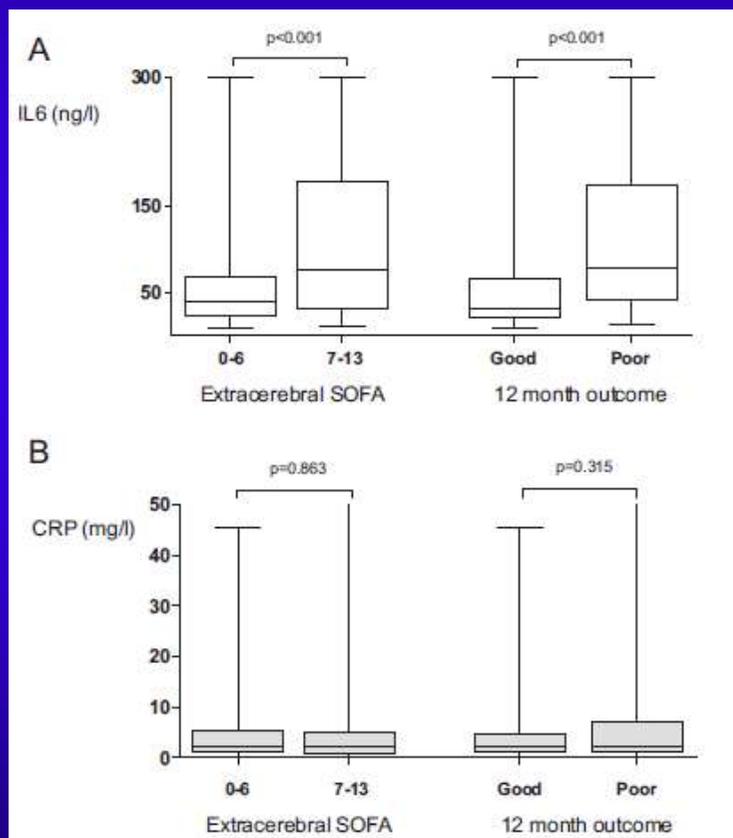


Figure 2. Measurement of endotoxin levels (endotoxin units

Clinical Paper

Admission interleukin-6 is associated with post resuscitation organ dysfunction and predicts long-term neurological outcome after out-of-hospital ventricular fibrillation[☆]

Jukka Vaahersalo^{a,*}, Markus B. Skrifvars^a, Kari Pulkki^b, Mats Stridsberg^c, Helge Røsjø^d, Seppo Hovilehto^e, Marjaana Tiainen^f, Tero Varpula^a, Ville Pettilä^a, Esko Ruokonen^g, the FINNRESUSCI Laboratory Study Group



Multiple logistic regression analysis for independent predictors of poor neurological outcome (CPC 3-5).

Variable	Adjusted odds ratio	95% confidence interval	p-value
Age (year)	1.055	1.014-1.097	0.008
ROSC (minute)	1.068	1.024-1.113	0.002
Coronary disease	0.427	0.171-1.068	0.069
Witnessed cardiac arrest	2.643	0.588-11.880	0.205
Admission IL-6 (ng/L)	1.006	1.000-1.011	0.046
Admission S-100B (µg/L)	2.453	0.809-7.435	0.113

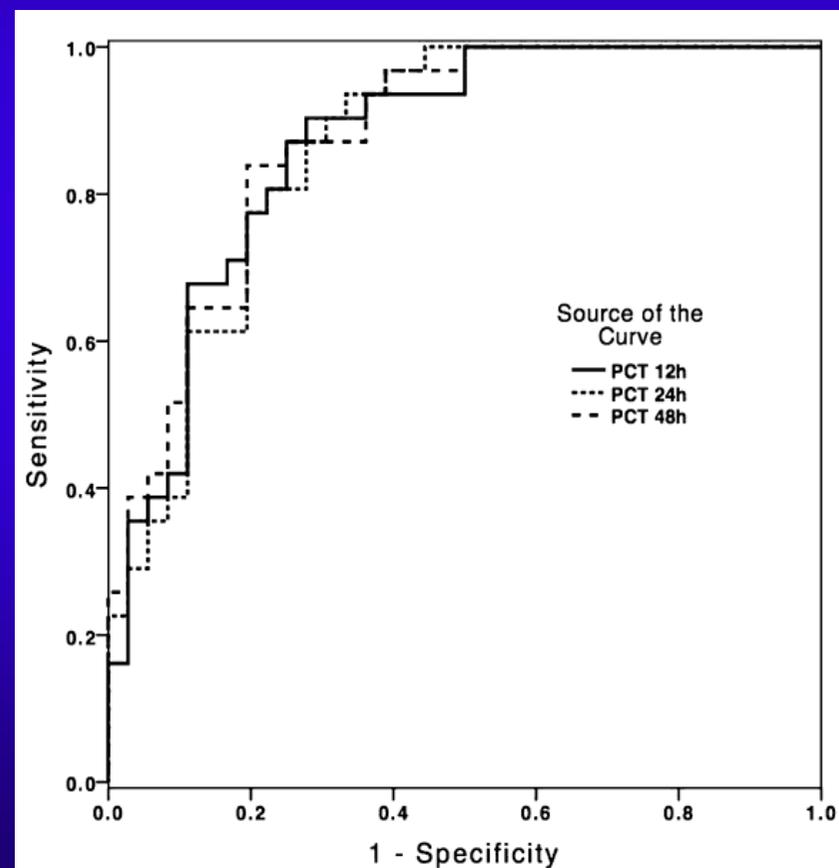
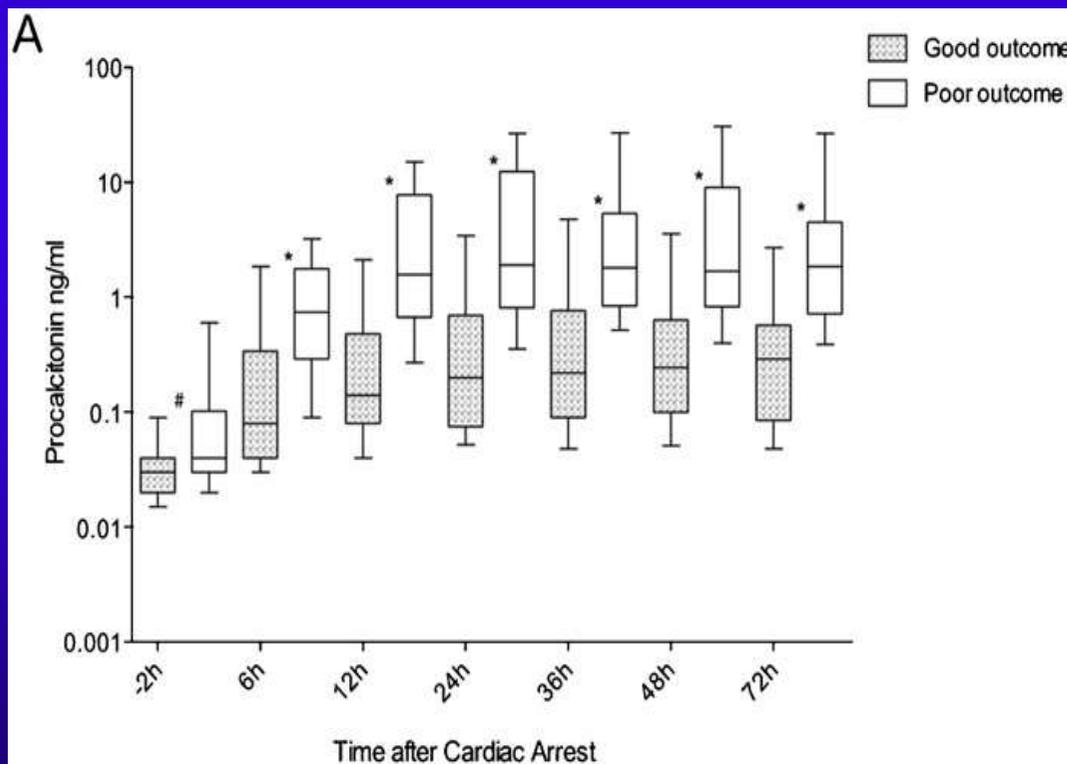
CPC; cerebral performance category, ROSC; return of spontaneous circulation, IL-6; interleukin-6.

Clinical paper

Procalcitonin after cardiac arrest – An indicator of severity of illness, ischemia-reperfusion injury and outcome[☆]

Martin Annborn^{a,*}, Josef Dankiewicz^a, David Erlinge^c, Sabine Hertel^b, Malin Rundgren^a, J. Gustav Smith^c, Joachim Struck^b, Hans Friberg^a

**Resuscitation
2013**



Factors associated with inflammatory biomarker levels

Variable	Reference Value	IL-1 β Multivariate Adjusted R ² = 0.05		IL-6 Multivariate Adjusted R ² = 0.11		Tumor Necrosis Factor- α Multivariate Adjusted R ² = 0.09		IL-4 Multivariate Adjusted R ² = 0.12		IL-10 Multivariate Adjusted R ² = 0.15		IL-13 Multivariate Adjusted R ² = 0.0	
		β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p	β (95% CI)	p
Age	Years		NS		NS		NS		NS		NS		NS
Sex	Male		NS		NS		NS		NS		NS		NS
Initial rhythm	Ventricular fibrillation/ ventricular tachycardia		NS		NS		NS		NS		NS		NS
Witnessed arrest	Yes	-4.8 (-9.2 to -0.3)	0.04		NS	-35.0 (-62.7 to -7.3)	0.01	-3.3 (-5.2 to -1.3)	0.001		NS		NS
Bystander cardiopulmonary resuscitation	Yes	-4.5 (-7.8 to -1.2)	0.008		NS	-35.0 (-54.7 to -15.2)	0.0006	-2.5 (-3.8 to -1.1)	0.0006		NS		NS
Time to return of spontaneous circulation	5 min		NS	53.3 (15.2-91.4)	0.006		NS		NS	22.2 (9.5-34.9)	0.0007		NS
ST-segment elevation myocardial infarction	Yes		NS		NS		NS		NS		NS		NS
Shock at admission	Yes		NS	677 (250-1104)	0.002		NS		NS	237 (97-378)	0.001		NS

Post Cardiac Arrest Inflammation

Complement activation

Cytokine release

Expression of adhesion molecules

Dysregulation of cytokine production by leukocytes

Presence of endotoxin in plasma

Microcirculatory alterations

Adrenal dysfunction

Coagulopathy

**Arresto
Cardiaco**

Stone heart, alterata contrattilità, edema, rigonfiamento mitocondriale

CPR

“no reflow”, stone heart

Fase post rianimazione

**Immediata
(ROSC -20 min)**

Disfunzione miocardica, ridotta gittata cardiaca

**Precoce
(fino a 6-12 ore)**

Disfunzione miocardica, citochine, miglioramento nel metabolismo cellulare

**Intermedia
(fino a 72 ore)**

Riduzione indice cardiaco, lento miglioramento funzionalità miocardica

**Recupero
(oltre le 72 ore)**

Miglioramento progressivo funzionalità miocardica

Reversible Myocardial Dysfunction in Survivors of Out-of-Hospital Cardiac Arrest

Ivan Laurent, MD,* Mehran Monchi, MD,* Jean-Daniel Chiche, MD,* Luc-Marie Joly, MD,* Christian Spaulding, MD,‡ Bénédicte Bourgeois, MD,† Alain Cariou, MD,* Alain Rozenberg, MD,† Pierre Carli, MD,† Simon Weber, MD,‡ Jean-François Dhainaut, MD, PHD*
 Paris, France

Table 2. Hemodynamic Data During the First 72 Hours

Hemodynamic Parameters	Interval From Onset of Cardiac Arrest to Measurement (h)						p Value§
	ICU Admission: 3.0 (2.0–3.6)	Time 0: 6.8 (4.3–7.3)	Time 1: 8.0 (7.0–9.0)	Time 2: 12.0 (11.0–13.5)	Time 3: 24.0 (23.0–25.7)	Time 4: 67.0 (52.0–72.0)	
Temperature (°C)	36.0 (35.4–36.7)	—	36.6* (35.8–37.5)	37.3† (36.7–38.1)	37.6† (37.0–38.2)	37.8† (37.3–38.3)	< 0.001
Epinephrine perfusion (mg/h)	0	0	1.0‡ (0–2.2)	1.3‡ (0–2.0)	1.5‡ (0–2.7)	0.4‡ (0–1.6)	0.042
HR (beats/min)	110 (89–123)	111 (91–124)	108 (97–125)	111 (98–128)	112 (101–125)	101* (94–120)	0.215
MAP (mm Hg)	87 (75–103)	62† (46–71)	79‡ (69–102)	76‡ (69–87)	80 (71–89)	80 (73–88)	0.04
MPAP (mm Hg)	—	—	28 (22–32)	24‡ (20–28)	24† (20–27)	28 (24–32)	0.005
RAP (mm Hg)	—	—	11 (8–15)	10 (8–13)	11 (8–13)	12 (9–15)	0.189
POAP (mm Hg)	—	—	14 (11–18)	12‡ (10–15)	13 (10–16)	14 (10–18)	0.248
CI (l/min per m ²)	—	—	2.05 (1.43–2.90)	2.61‡ (1.90–3.46)	3.19‡ (2.67–4.20)	3.69* (2.92–4.49)	< 0.001
SVRI (dynes/cm ⁵ ·m ²)	—	—	2,908 (1,946–4,658)	1,936† (1,493–2,951)	1,672† (1,300–2,034)	1,518† (1,153–1,852)	< 0.001
PVRI (dynes/cm ⁵ ·m ²)	—	—	438 (339–593)	363† (221–488)	261† (183–346)	274* (206–371)	< 0.001
SI (ml/m ²)	—	—	20.0 (15.0–23.8)	22.5‡ (18.4–32.1)	29.3† (24.8–37.4)	35.3‡ (28.5–42.1)	< 0.001
LVSWS (g·m/m ²)	—	—	23.8 (19.3–31.0)	24.5 (19.8–34.9)	33.3† (25.0–43.1)	41.1‡ (31.4–50.0)	< 0.001

*p < 0.05, †p < 0.001, ‡p < 0.01 for all tests performed versus baseline. Baseline values were at intensive care unit (ICU) admission for temperature, epinephrine infusion, and heart rate; time 0 for mean arterial pressure (MAP); and time 1 for the other values. Mean arterial pressure at admission and time 0 was determined by noninvasive methods, and MAP at times 1, 2, 3, and 4 by invasive monitoring. §The p value in the last column refers to nonparametric analysis of variance (Kruskal-Wallis test). Data are presented as the median value (interquartile range).

CI = cardiac index; HR = heart rate; LVSWS = left ventricular stroke work; MPAP = mean pulmonary artery pressure; POAP = pulmonary occlusion arterial pressure; PVRI = pulmonary vascular resistance index; RAP = right arterial pressure; SI = stroke index; SVRI = systemic vascular resistance index.

Meccanismi di disfunzione miocardica

MECCANISMI I

Ischemia miocardica globale

↑ Lattato ↑ CO₂ ↑ H⁺

Scambio Na⁺- Ca²⁺

↓ Canali voltaggio dipendenti Ca²⁺

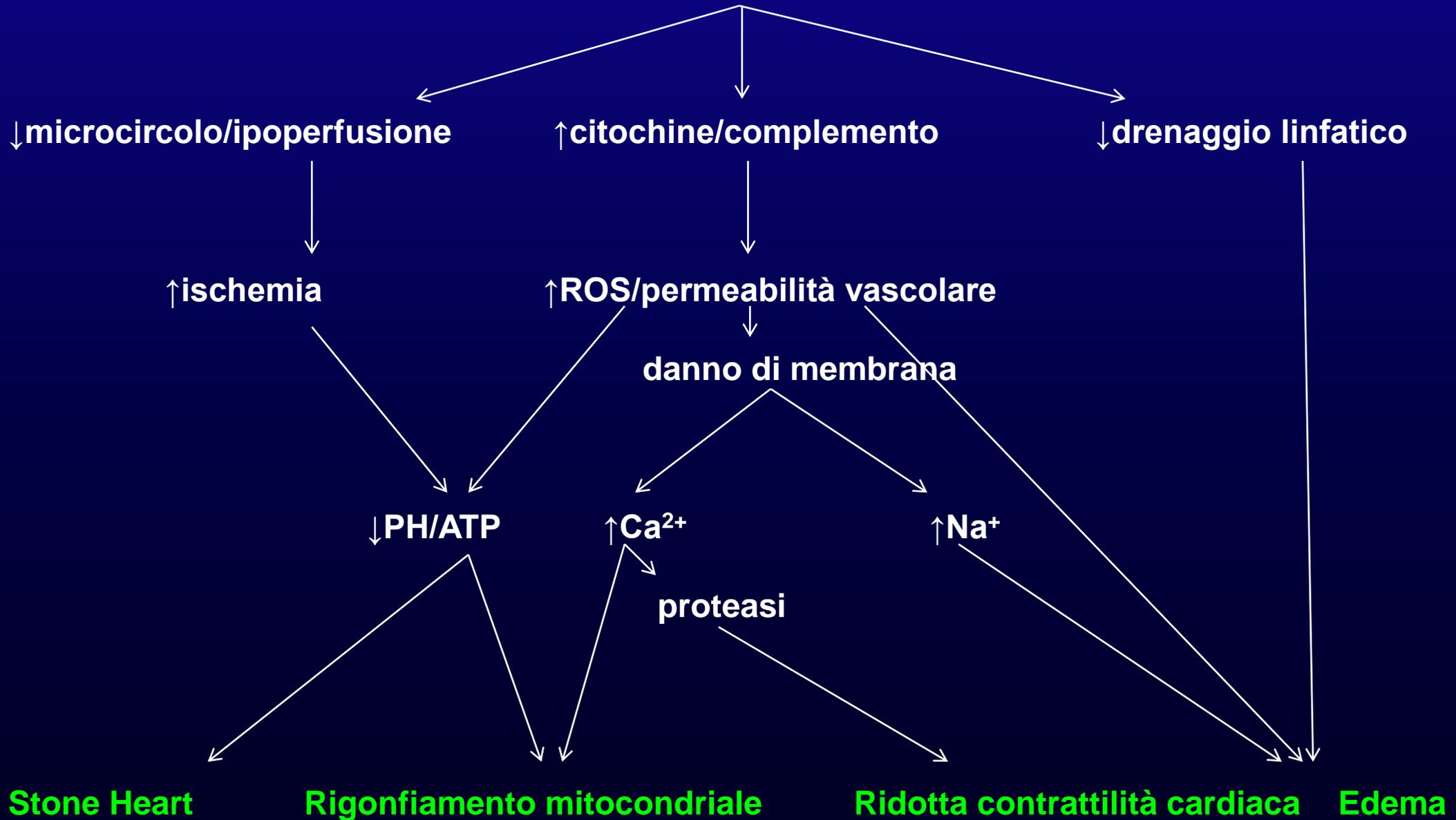
↑ Apertura canali Ca²⁺

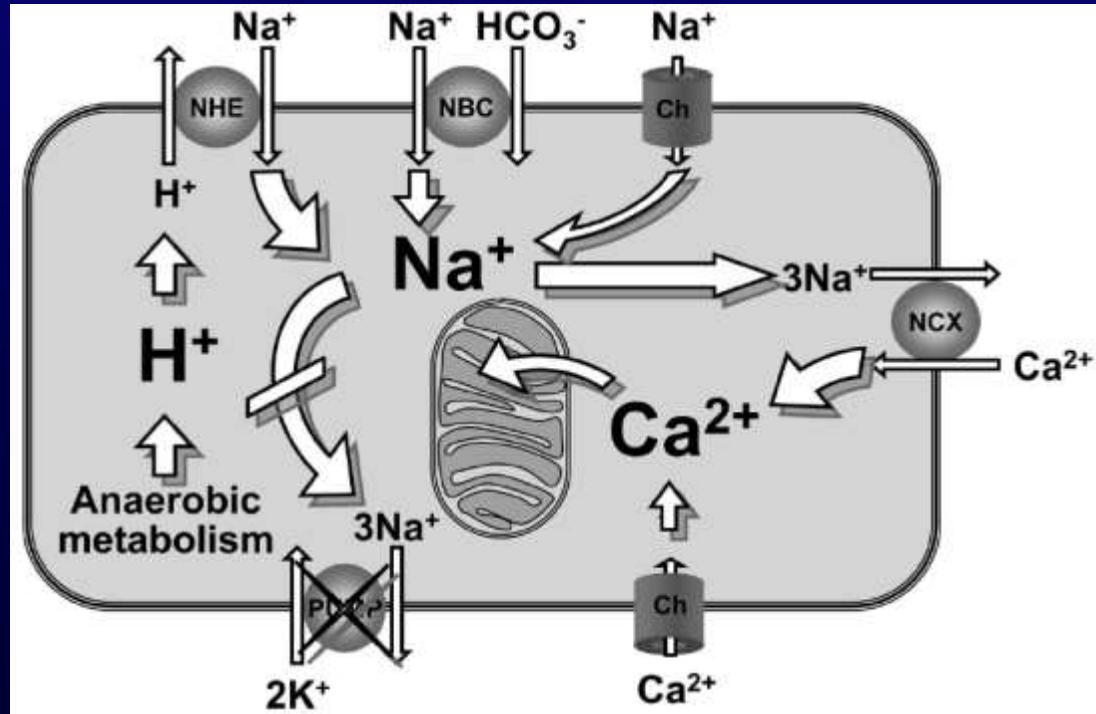
Sovraccarico intracellulare Ca²⁺

↓ Capacità di legame actina-miosina

↓ Funzione mitocondriale

Arresto Cardiac/Riperfusione



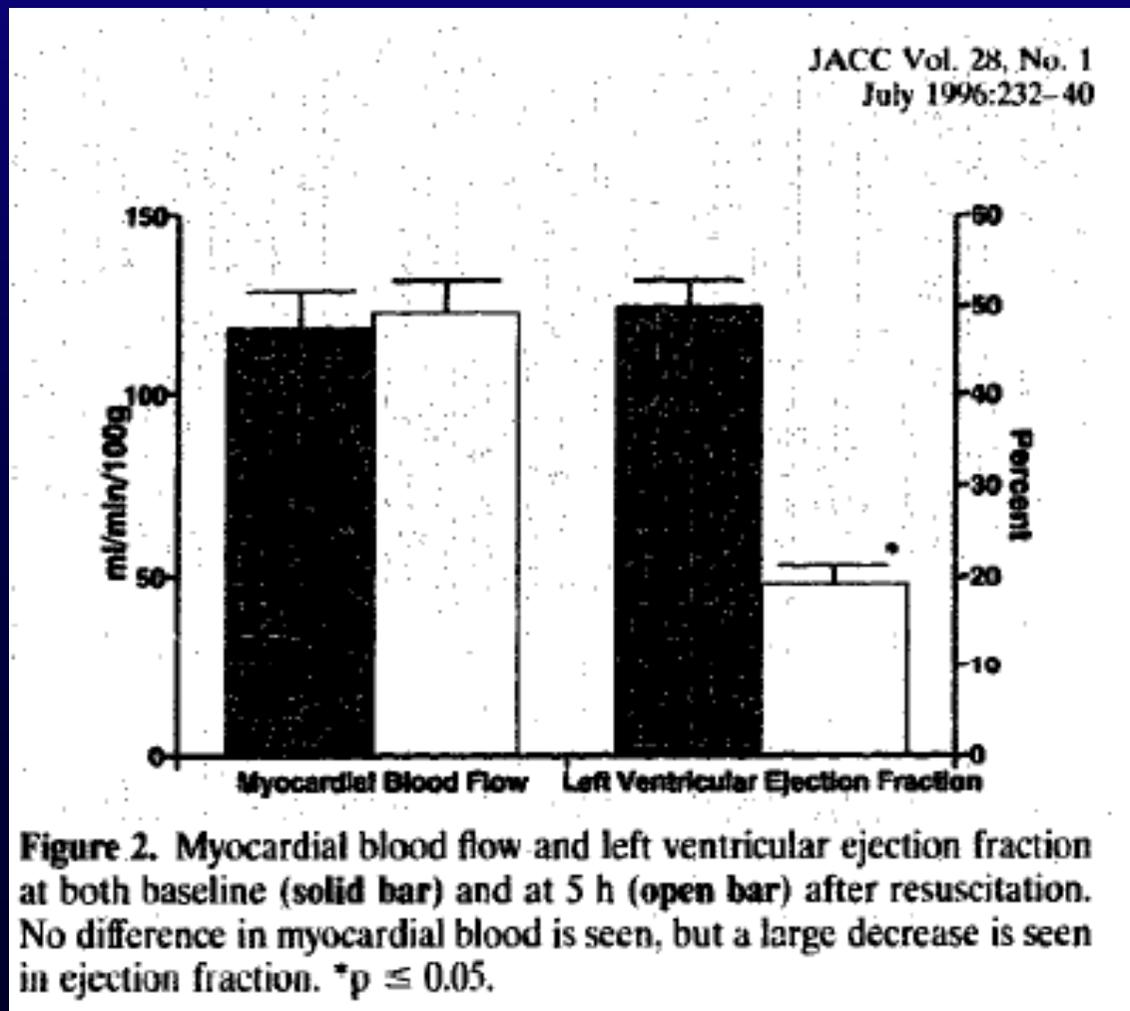


Rappresentazione schematica di un cardiomiocita durante ischemia e riperfusione. Si osserva il sovraccarico di calcio citosolico e mitocondriale indotto da Na⁺. NHE=Na⁺/H⁺; NBC=scambiatore Na⁺/HCO₃⁻; NCX=scambiatore Na⁺/Ca²⁺; Ch=canale (Per gentile concessione del dottor Ayoub).

Meccanismi dell'ischemia riperfusione miocardica

- **Alterazione ioni intracellulari:** sovraccarico Ca^{2+} intracellulare; sovraccarico Na^{+} intracellulare; Acidosi intracellulare
- **Alterazione del potenziale di membrana mitocondriale**
- **Formazione di radicali liberi dell'ossigeno (ROS):** generazione di xantine ossidasi; rilascio di prodotti intermedi reattivi mitocondriali; infiltrazione di neutrofili; ROS indotti dai ROS
- **Alterazioni del metabolismo del ossido nitrico (NO):** perdita della vasodilatazione NO indotta; accumulo di nitrati
- **Apoptosi**
- **Disfunzione endoteliale:** attivazione citochine e chemochine; espressioni di fattori di adesione cellulare; alterazione meccanismi di vasodilatazione
- **Aggregazione piastrinica e microembolizzazioni**
- **Attivazione immunità:** immunità innata (attivazione complemento, espressione di recettori del toll like); accumulo di neutrofili; danno mediato dall'infiltrazione (macrofagi e T cell).

Stunning miocardico

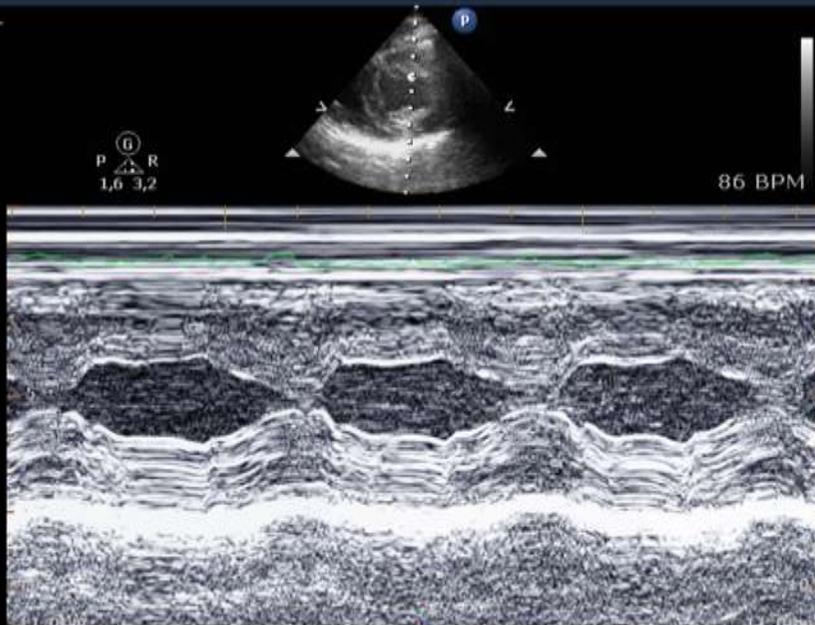


PHILIPS MAIALE_GR_12 BL MI 1,3 09/11/2015
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MAIALE S5-
S5-1
38 Hz
11,0cm

2D
HGen
Gn 65
C 47
5/1/1

M-mode
3/1
100 mm/s



MAIALE_GR_12 BL PHILIPS MAIALE_GR_07 4H MI 1,3 02/10/2015
EXP MAIALE ARGON 2 EXP MAIALE ARGON 2 02102015 4H IST.RIC. TIS 0,6 16:32:30

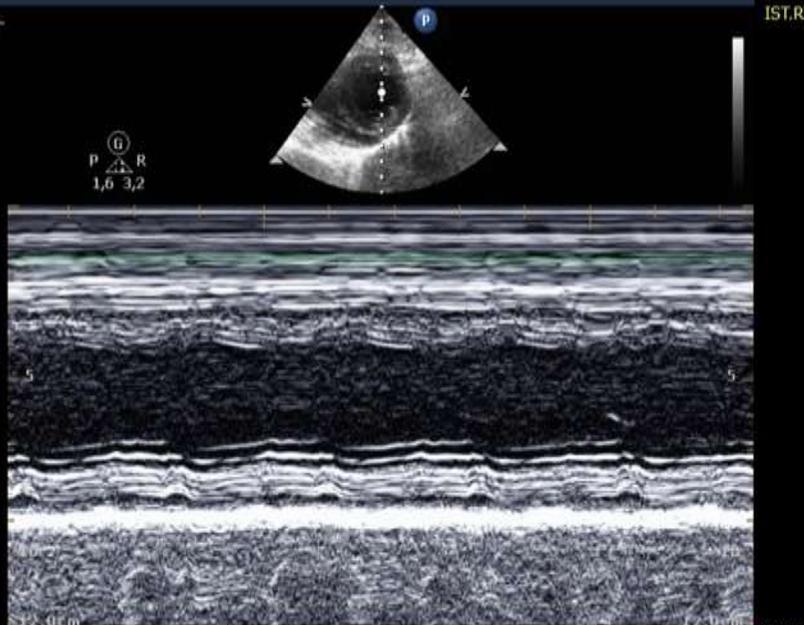
IST.RIC. MARIO NEGRI

MAIALE S5-
S5-1
4 Hz
2,0cm

D
HGen
Gn 35
C 47
5/1/1

I-mode
3/1
100 mm/s

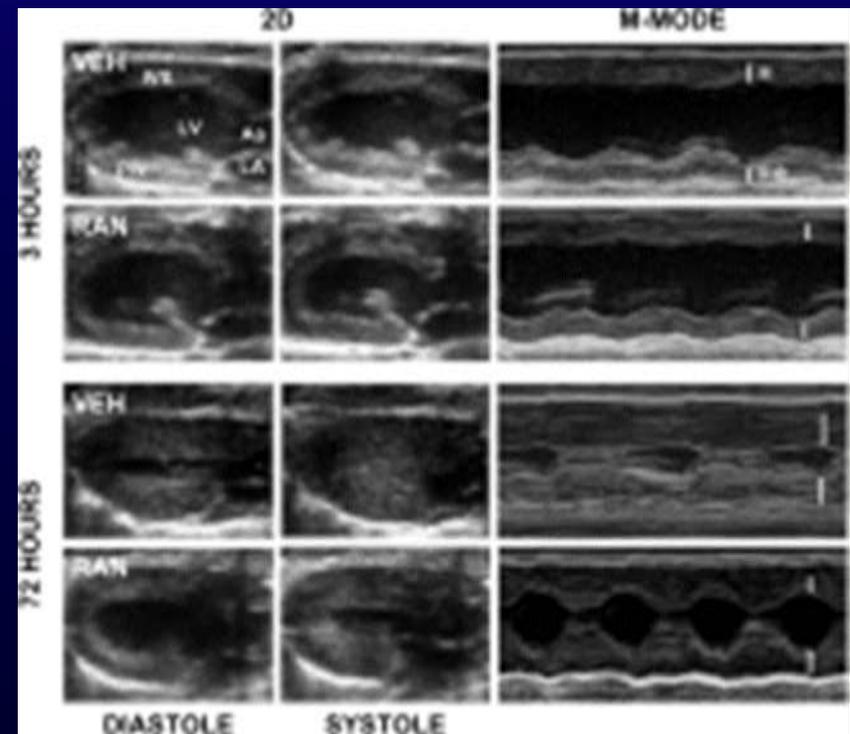
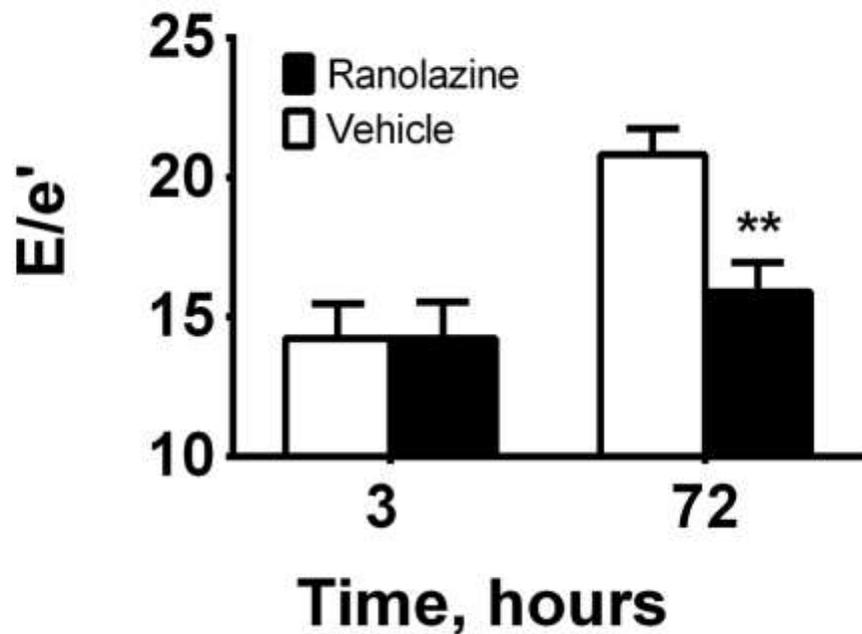
09/11/2015 12:33:33



02/10/2015 16:32:30

④ Ranolazine ameliorates postresuscitation electrical instability and myocardial dysfunction and improves survival with good neurologic recovery in a rat model of cardiac arrest

Francesca Fumagalli, MBIotech[†], Ilaria Russo, MBiol[†], Lidia Staszewsky, MD[†], Yongqin Li, MSEE, PhD[†], Teresa Letizia, MD[‡], Serge Masson, PhD[†], Deborah Novelli, MBiol[†], Marcella Rocchetti, PhD[§], Mara Canovi, PhD[†], Pietro Veglianesi, PhD[†], Marco Gobbi, PhD[†], Roberto Latini, MD[†], Antonio Zaza, MD[§], Giuseppe Ristagno, MD, PhD[†] 🌱 📧

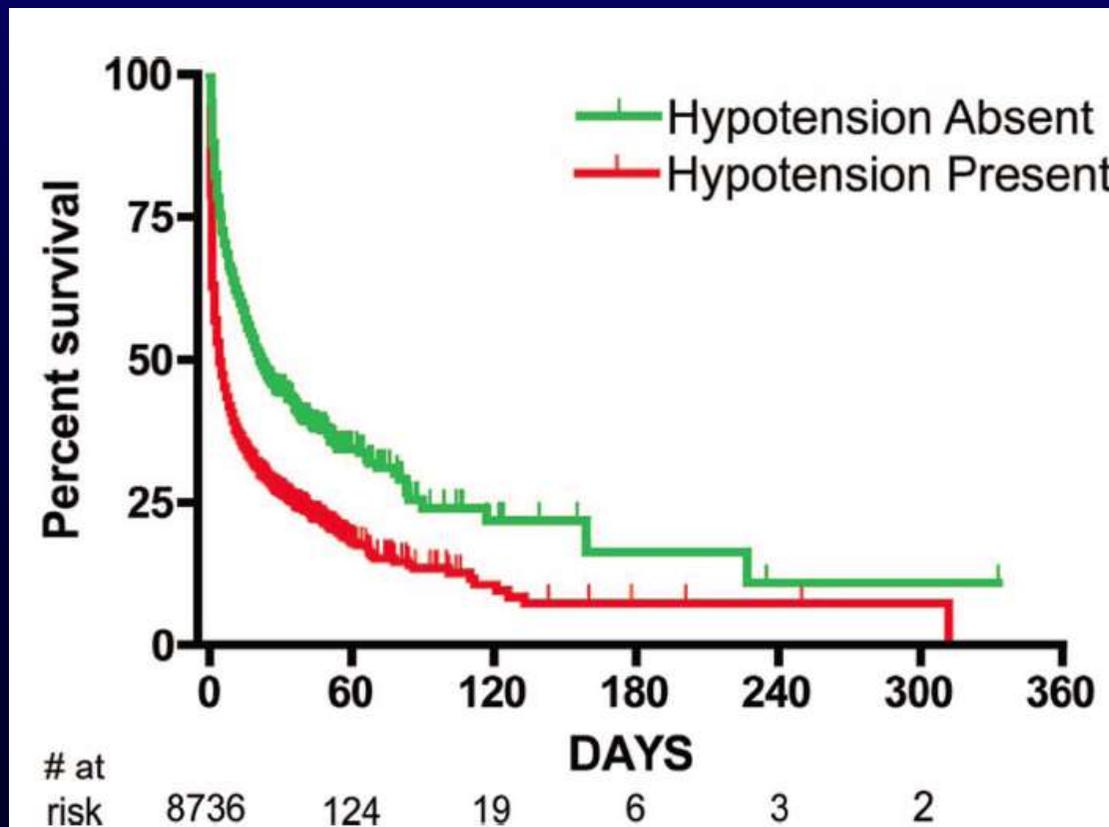


Endpoint cardiovascolari

- Non noto reale endpoint di pressione arteriosa
 - PAM >65 (?)
 - Considerare valori pressori anamnestici
- Importante evitare ipoperfusione d'organo:
 - Clearance lattati
 - SvcO₂
 - Diuresi adeguata

Significance of arterial hypotension after resuscitation from cardiac arrest*

Stephen Trzeciak, MD, MPH; Alan E. Jones, MD; J. Hope Kilgannon, MD; Barry Milcarek, PhD; Krystal Hunter, MBA; Nathan I. Shapiro, MD, MPH; Steven M. Hollenberg, MD; R. Phillip Dellinger, MD; Joseph E. Parrillo, MD





Clinical Paper

Hemodynamic targets during therapeutic hypothermia after cardiac arrest: A prospective observational study^a



K. Ameloot^{a,*,1}, I. Meex^{b,c,1}, C. Genbrugge^{b,c}, F. Jans^{b,c}, W. Boer^b, D. Verhaert^a,
 W. Mullens^{a,c}, B. Ferdinande^a, M. Dupont^a, C. De Deyne^{b,c}, J. Dens^{a,c}

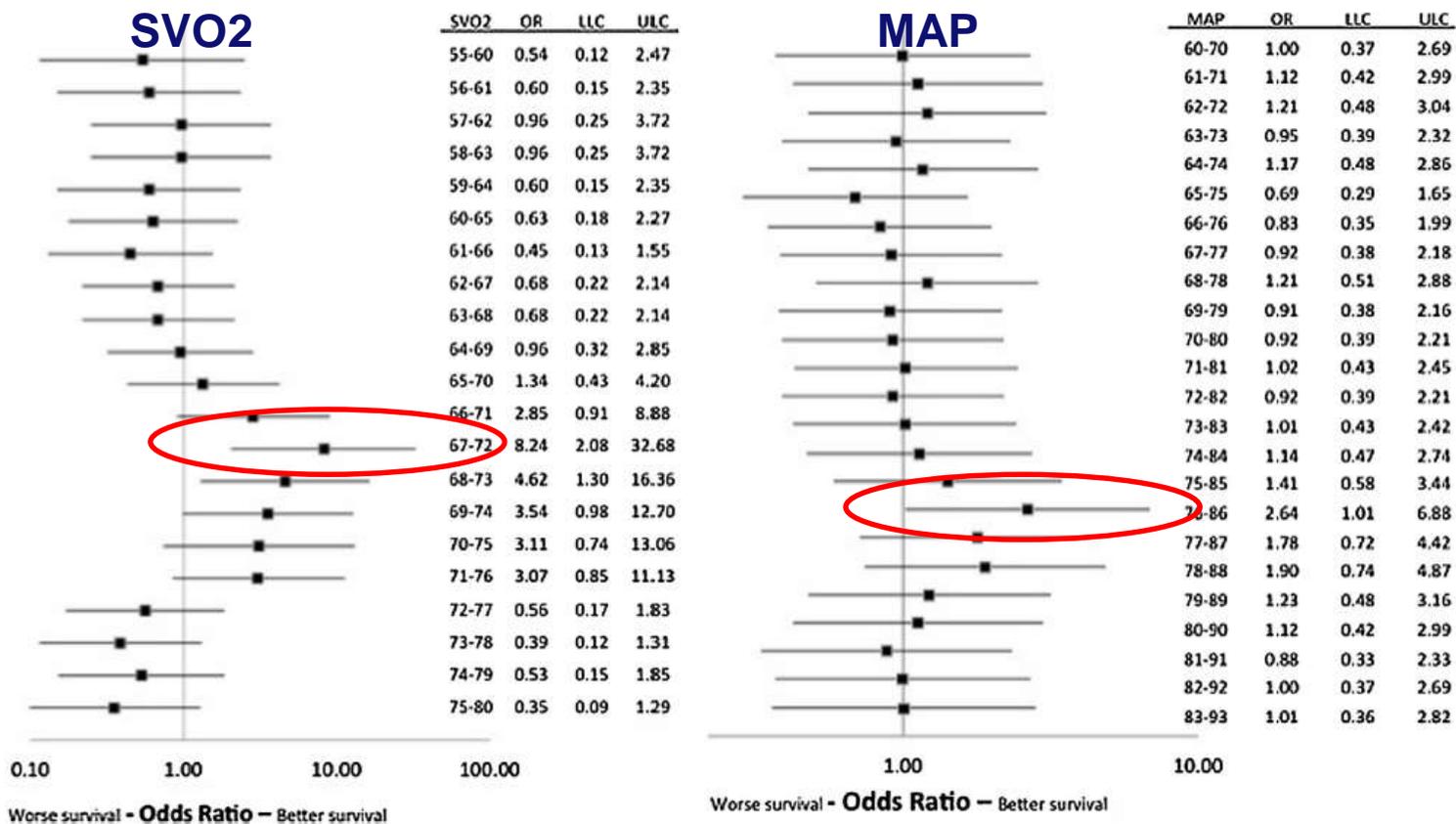
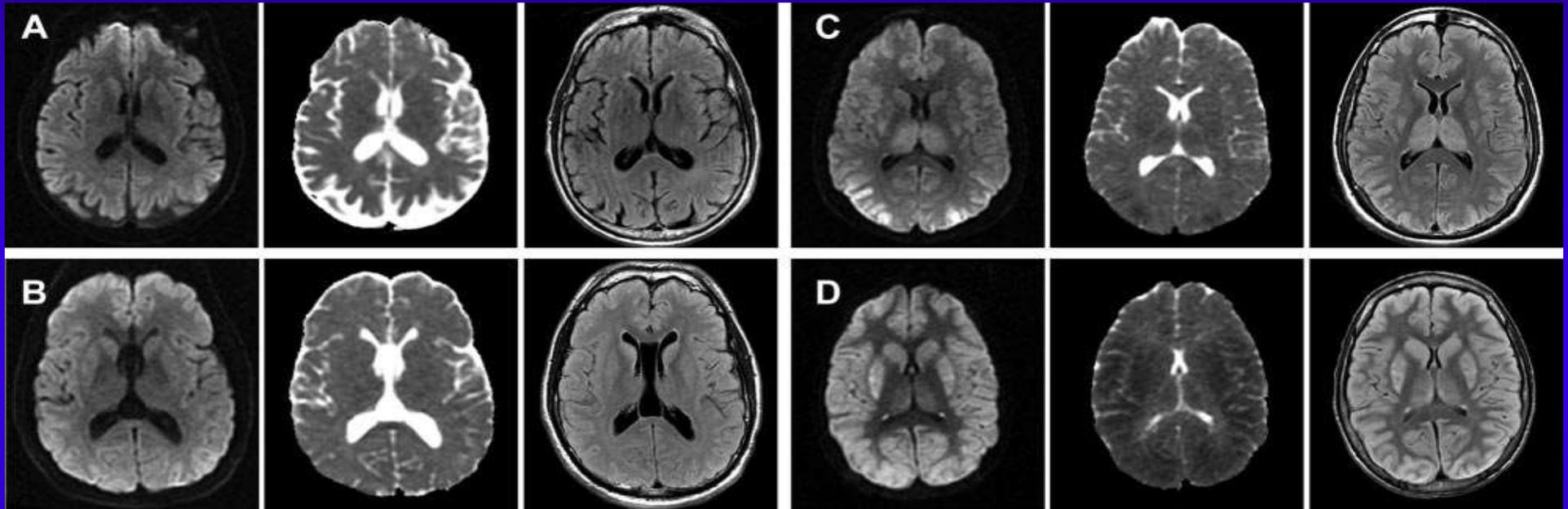


Fig. 1. Forest plot (a) Odds ratios for survival per 5% SVO₂ and (b) Odds ratios for survival per 10 mmHg MAP.



Mlynash M, Campbell DM, Leproust EM, Fischbein NJ, Bammer R, Eyingorn I, Hsia AW, Moseley M, Wijman CA. Temporal and spatial profile of brain diffusion-weighted MRI after cardiac arrest. *Stroke*. 2010 Aug;41(8):1665-72.

Arresto Cardiaco

Assenza di flusso



RCP



ROSC

Danno da riperfusione

•A livello cellulare CEREBRALE

Danno da riperfusione

•A livello SISTEMICO

Basso flusso



Danno cerebrale primario



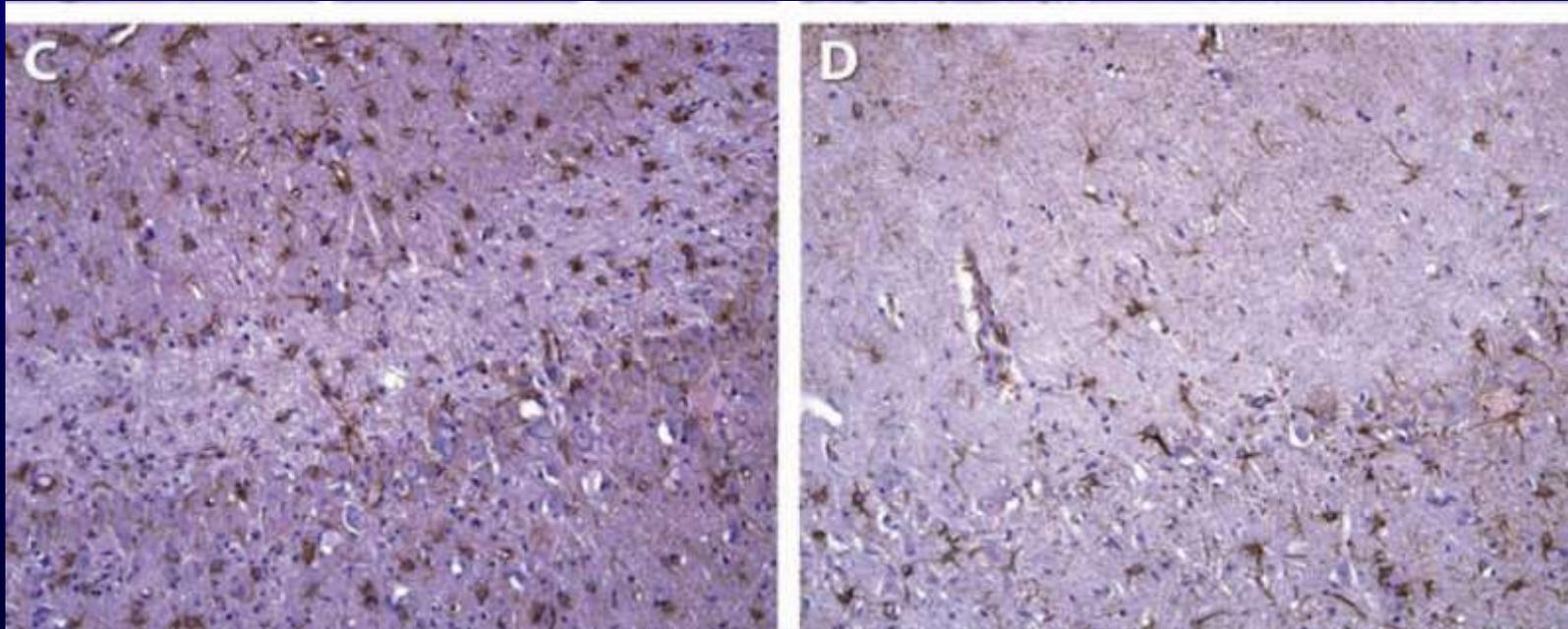
Danno cerebrale secondario



Danno cerebrale definitivo



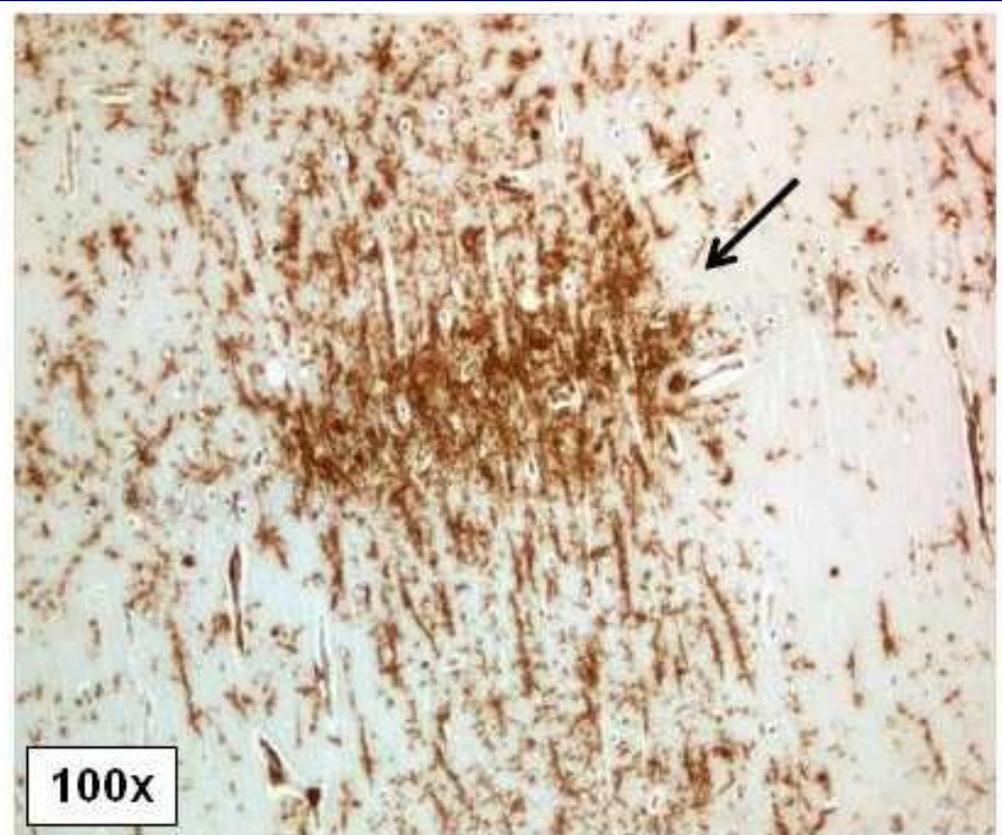
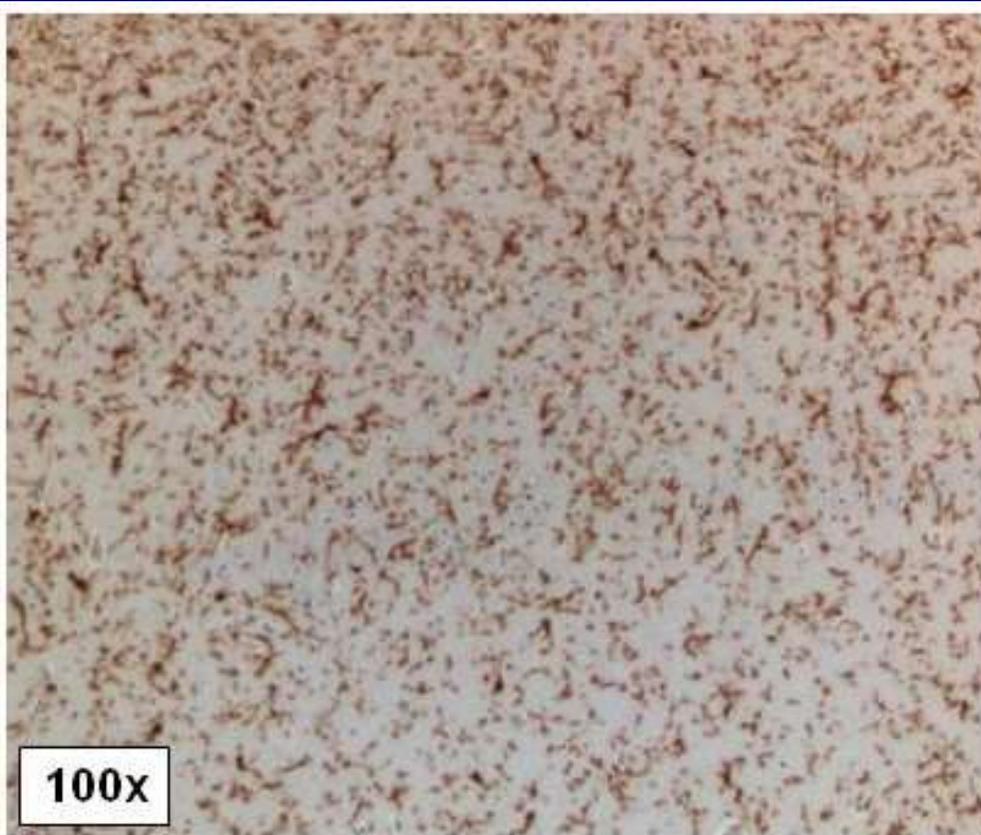
Immunohistochemical staining of the hippocampal CA 1 region with glial fibrillary acidic protein reveals pronounced astrogliosis



Cardiac Arrest Duration: 8 minutes

Control

CPR



IBA1 IHC-staining, 100x, Pig, Brain,
hippocampus, CA1, #7,
Non-activated microglia

IBA1 IHC-staining, 100x, Pig, Brain,
hippocampus, CA1, #5,
Microglia activation

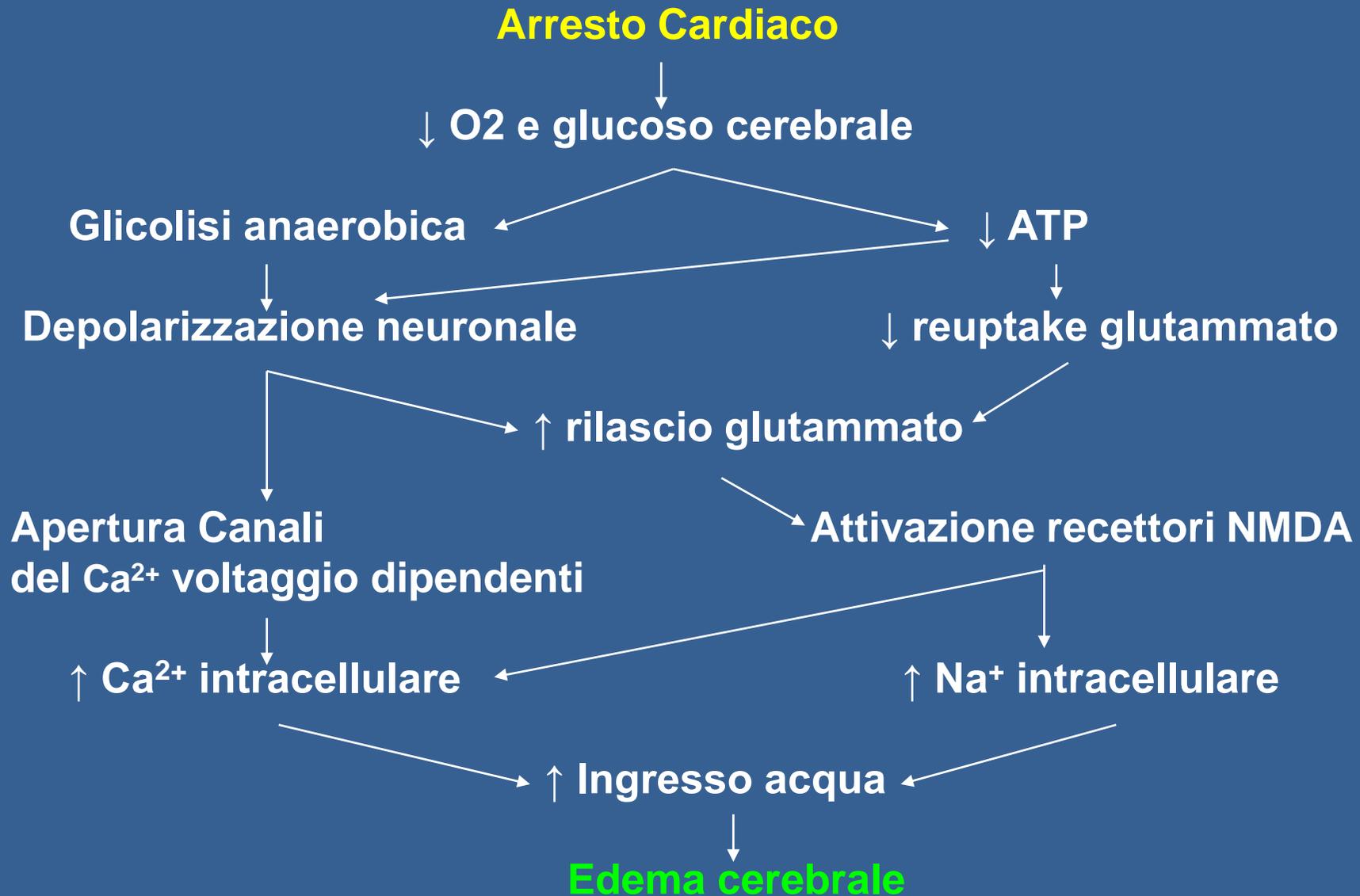
Il cervello è un organo particolarmente delicato, con una scarsissima tolleranza all'ischemia ed una risposta peculiare alla riperfusione.

Le aree cerebrali più suscettibili all'ischemia:

- Ippocampo
- Corteccia
- Cervelletto
- Corpo striato e talamo.

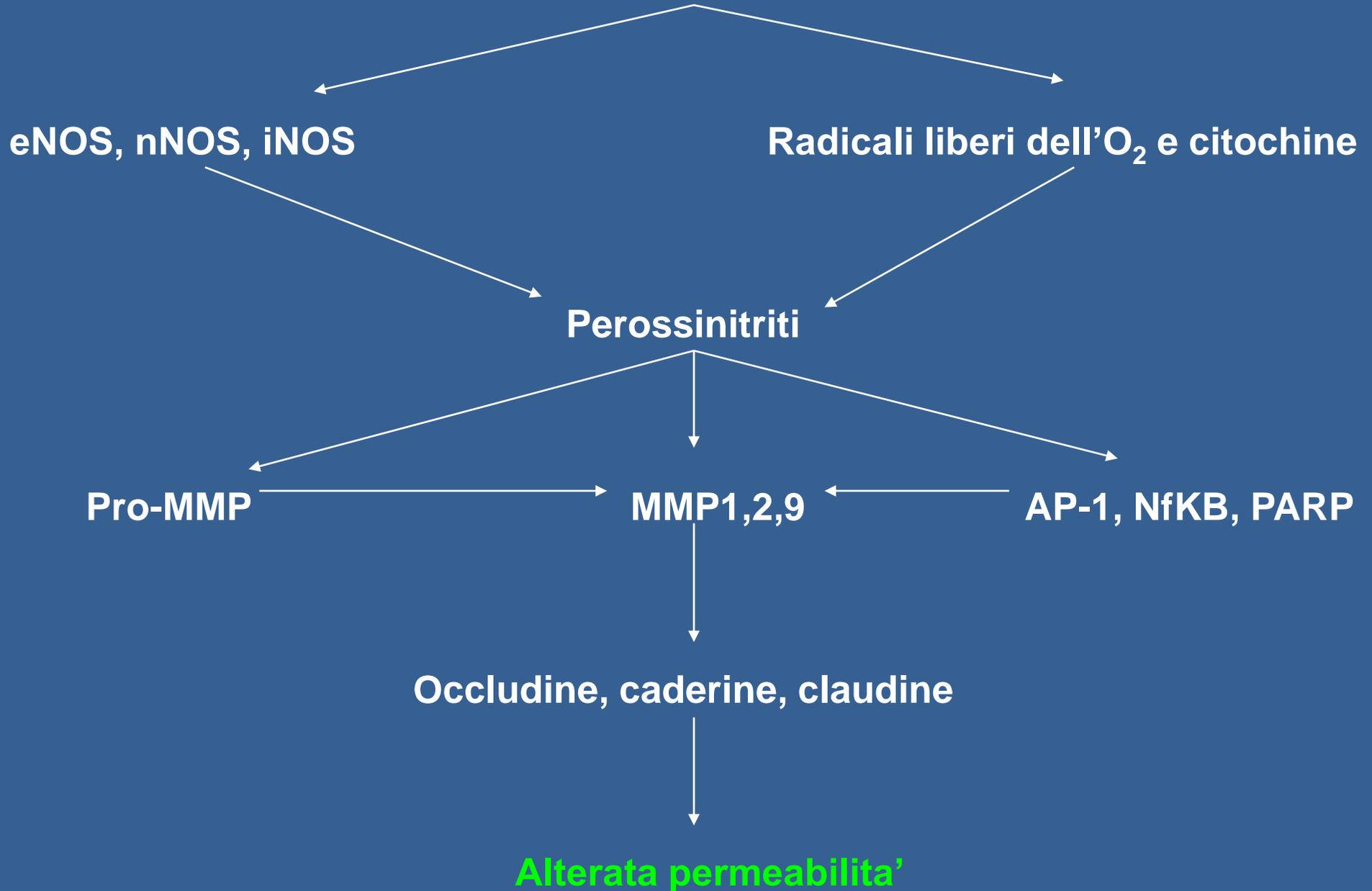
L'entità del danno dipende:

- Durata dell'arresto cardiaco "non trattato"
- Durata dell'RCP
- Età del paziente
- Presenza di comorbidità.



Xiao F. Bench to bedside: brain edema and cerebral resuscitation: the present and future. Acad Emerg Med 2002; 9.

Arresto Cardiaco



I meccanismi coinvolti nel danno cerebrale sono innumerevoli e complicati, tra questi l'eccitotossicità, l'alterata omeostasi dello ione calcio, la formazione di ROS e l'attivazione dei processi di apoptosi e necrosi cellulare sono i più importanti

Nella fase di ischemia:

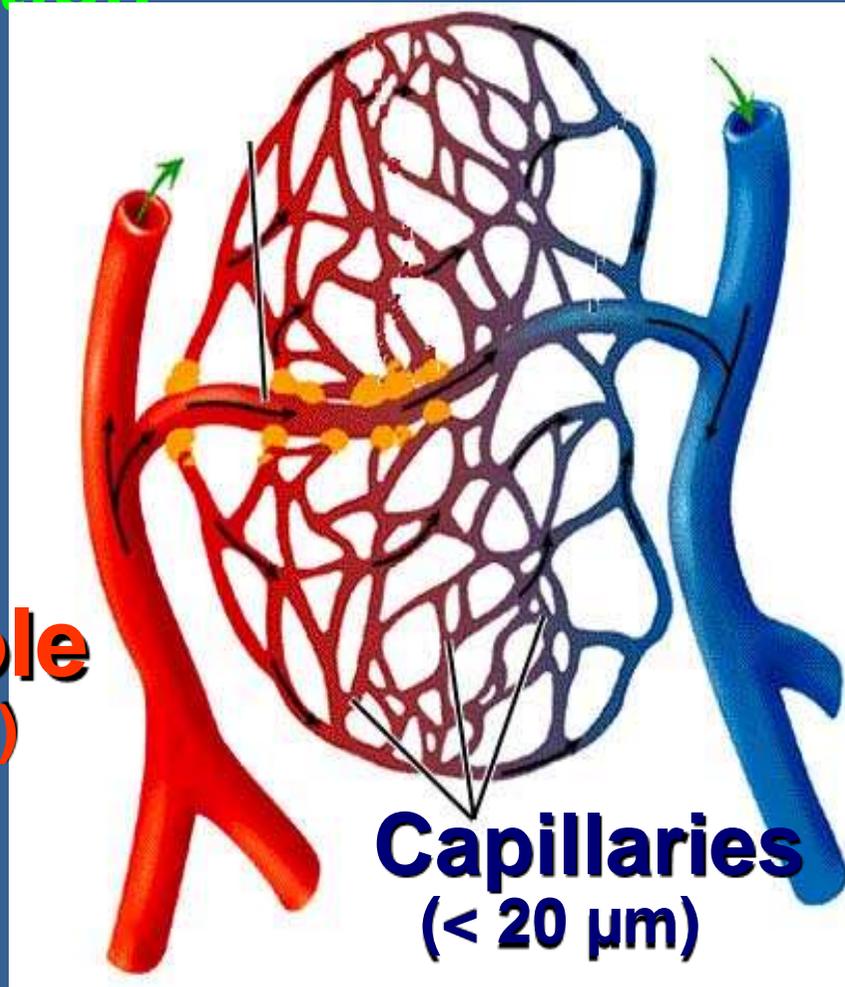
depolarizzazione cellulare → rilascio di glutammato → incremento dello Ca^{2+} intracellulare → liberazione del citocromo C → cascata apoptotica.

Nella fase di riperfusione:

- Stress ossidativo, attivazione di citochine proinfiammatorie, reclutamento di neutrofili.
- Alterazioni trombotiche nel microcircolo cerebrale -> incompleta riperfusione → prolungamento dell'ischemia tissutale.
- Edema cerebrale.

Both cardiac arrest and sepsis are thought to involve multi-organ ischemic injury and microcirculatory dysfunction

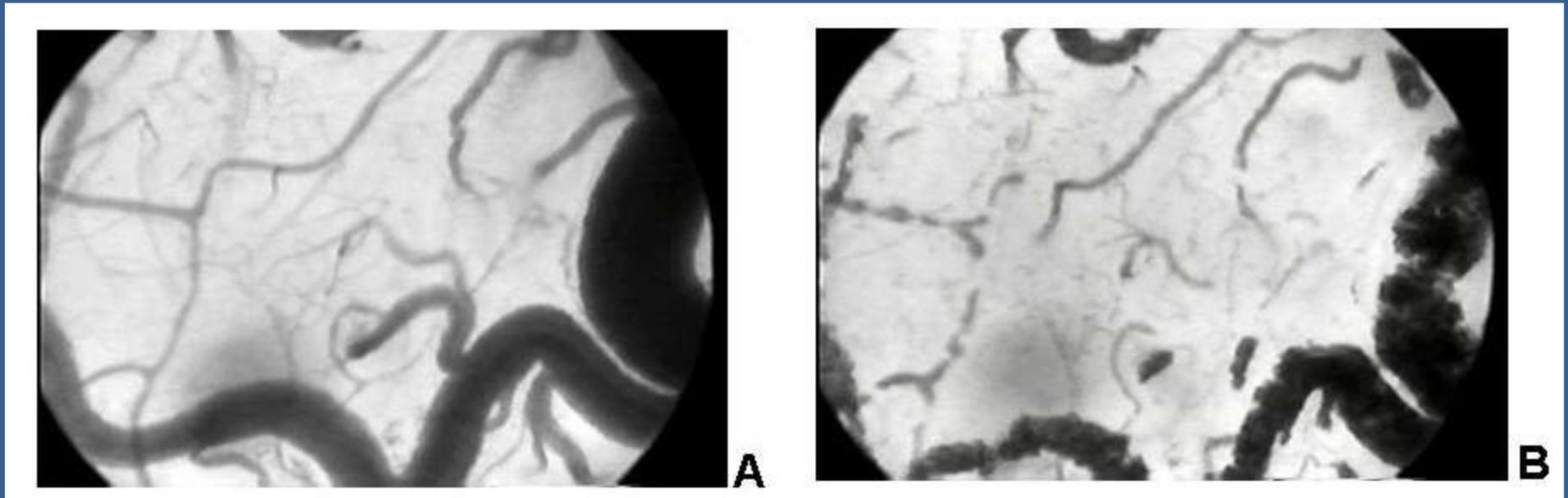
Arteriole
($> 20 \mu\text{m}$)



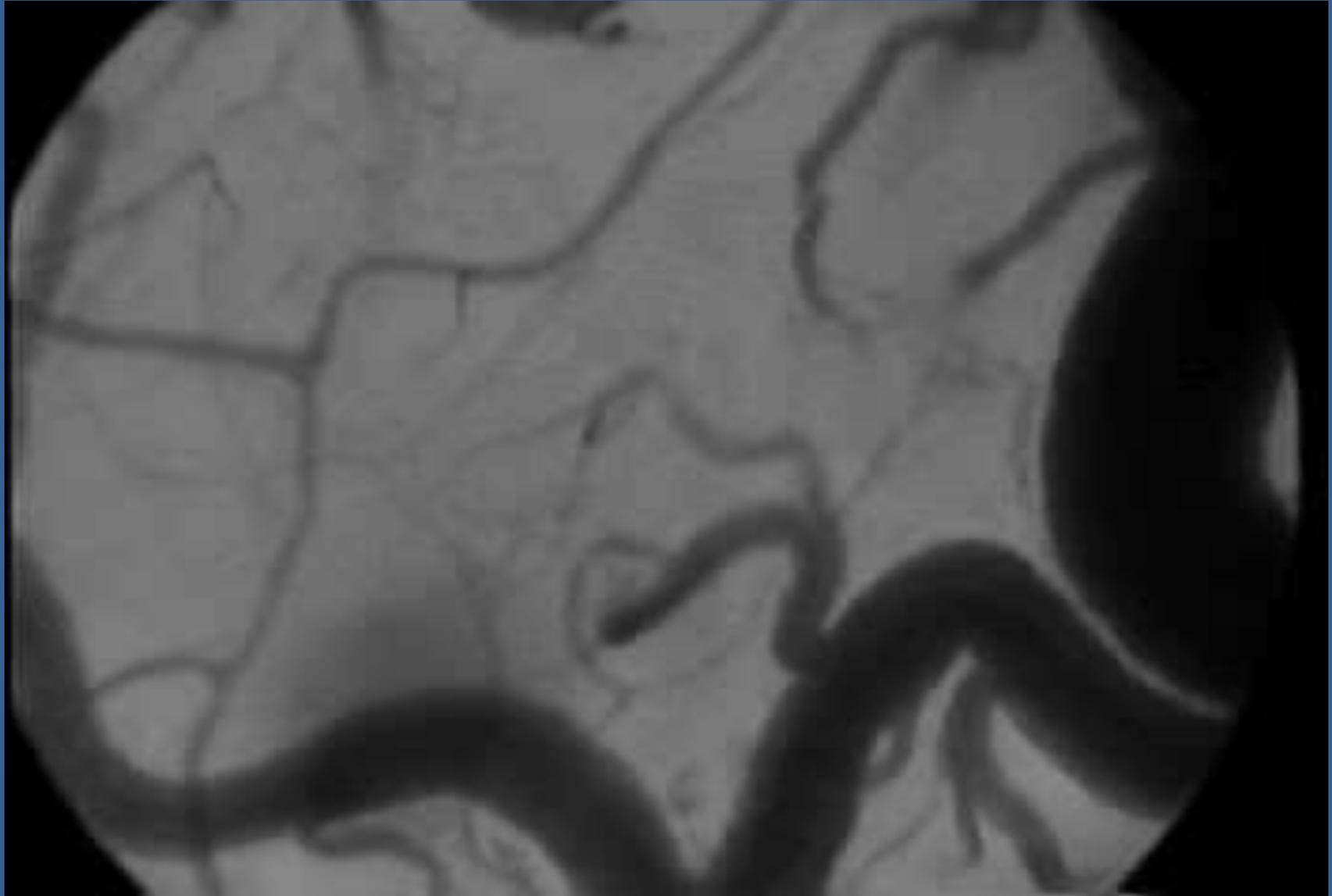
Capillaries
($< 20 \mu\text{m}$)

Venule
($> 20 \mu\text{m}$)

Arresto cardiaco e Microcircolazione

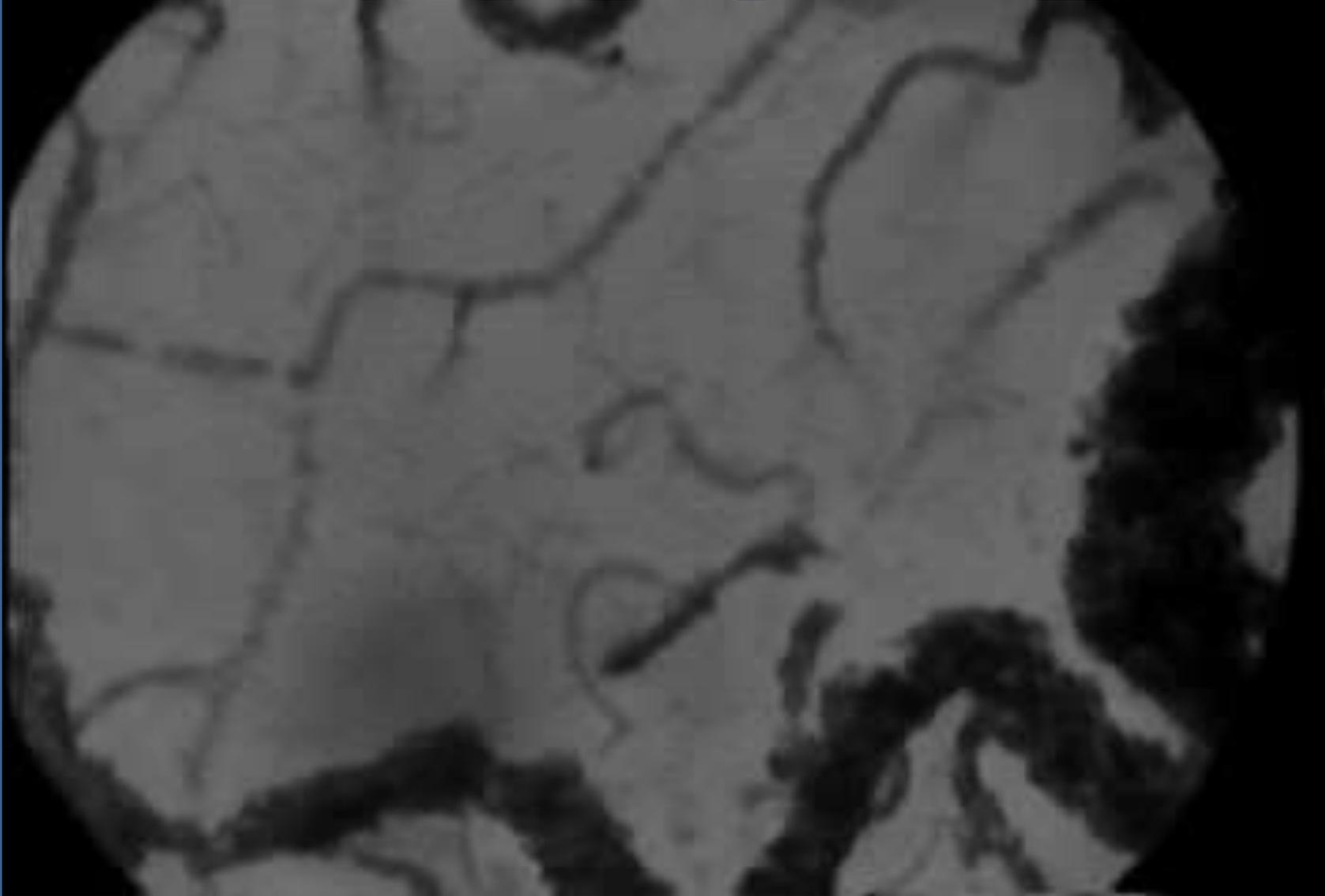


Cortical MBF before Cardiac Arrest



Baseline

Cortical MBF during Cardiac Arrest



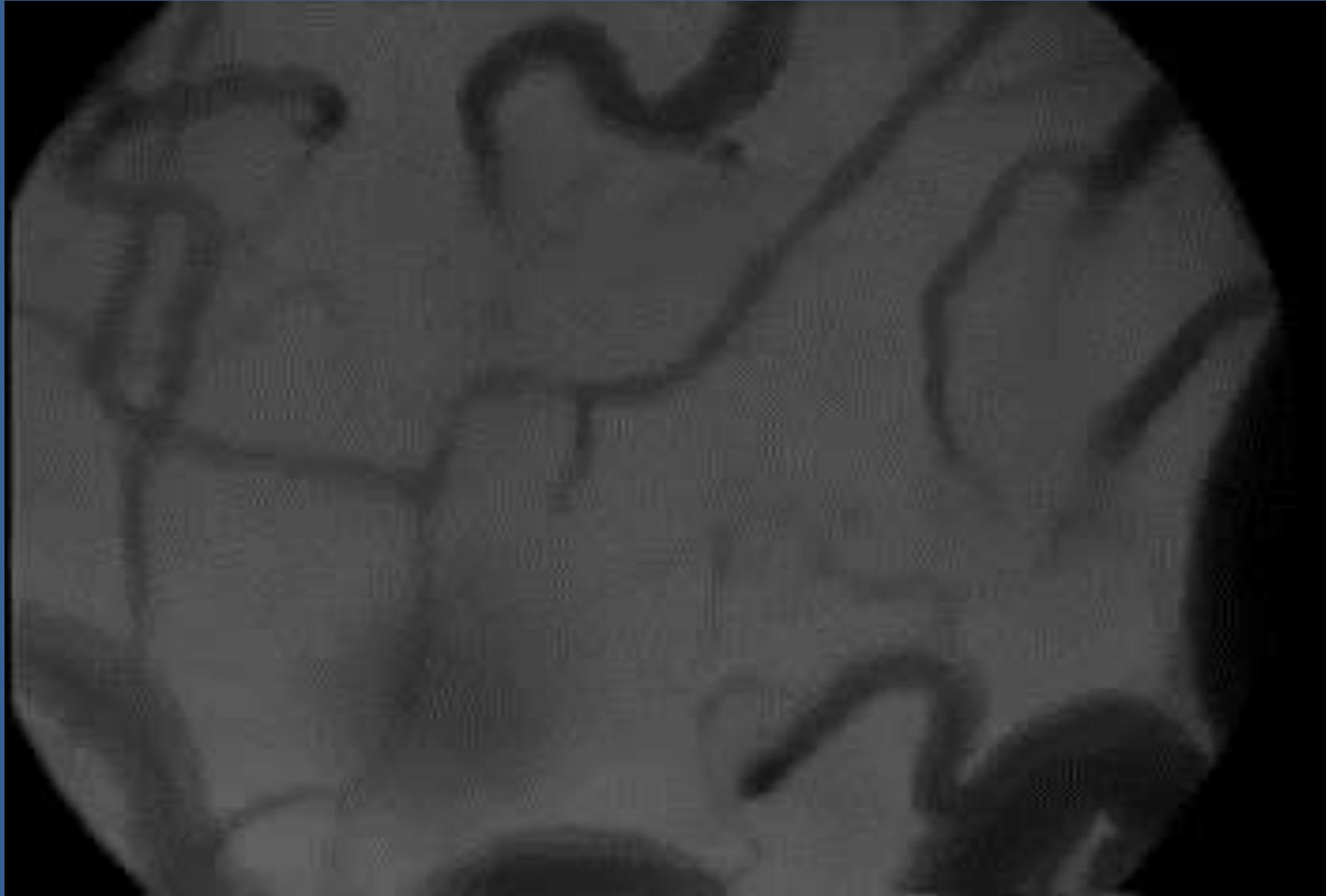
Ventricular Fibrillation 1 min

Cortical MBF during Cardiac Arrest



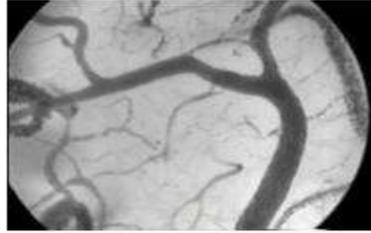
Ventricular Fibrillation 2 min

Cortical MBF after Resuscitation

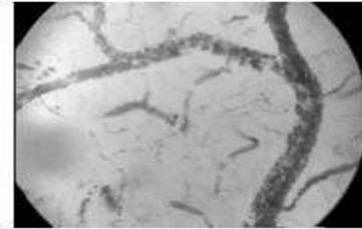


PR 3 min

Baseline



Cardiac Arrest

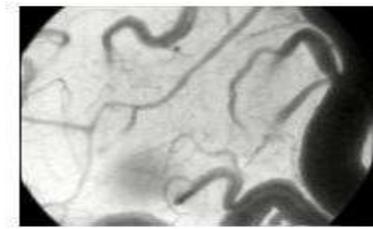


Epinephrine

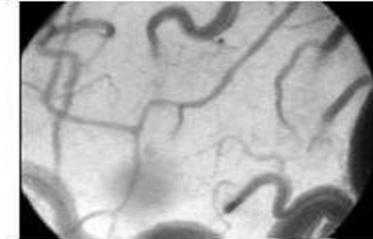
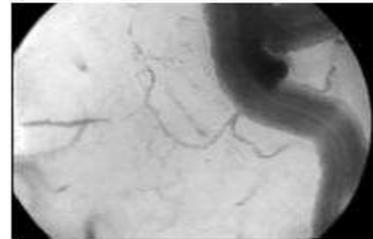
Placebo

Post Resuscit.
minutes

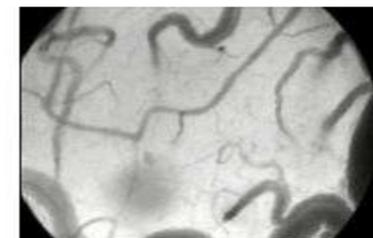
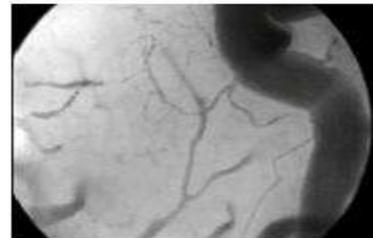
1



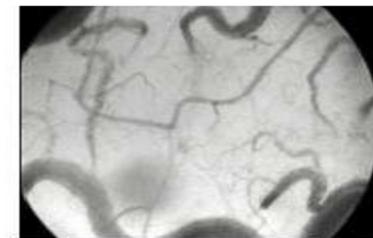
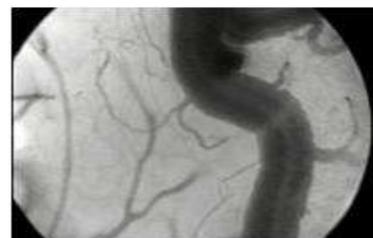
3



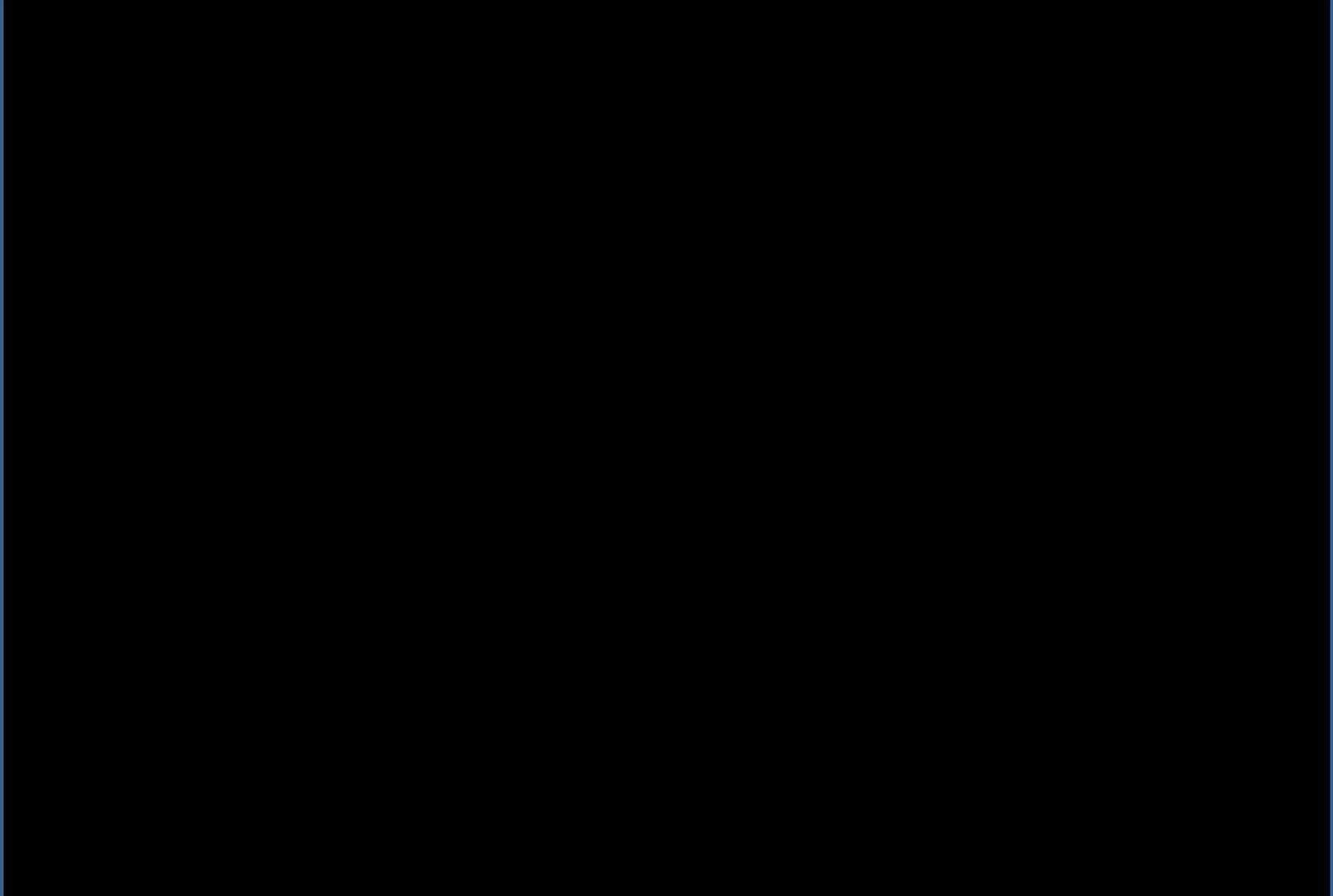
5



7



Post Resuscitation



PR 3 min

Epinephrine

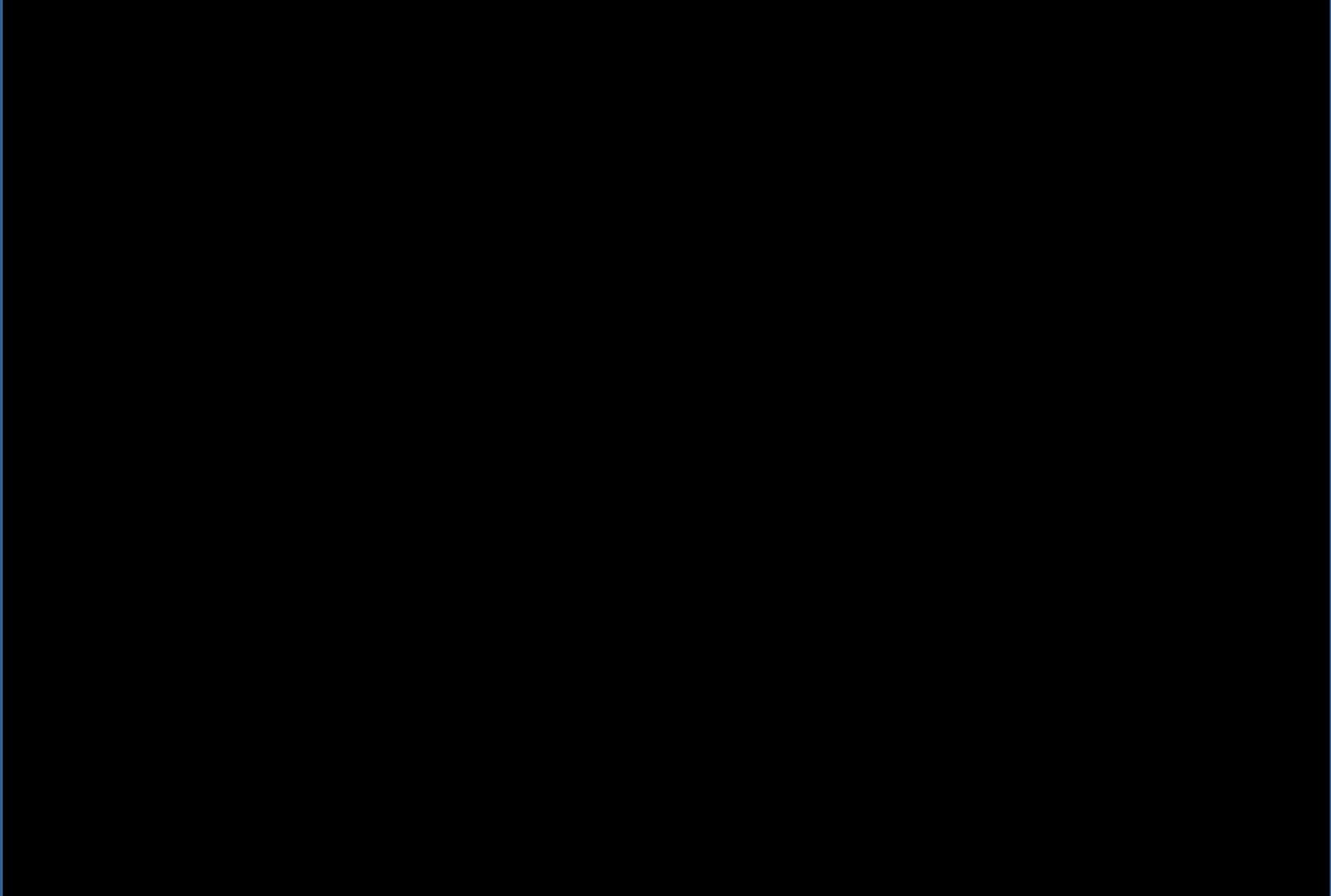
Post Resuscitation



PR 5 min

Epinephrine

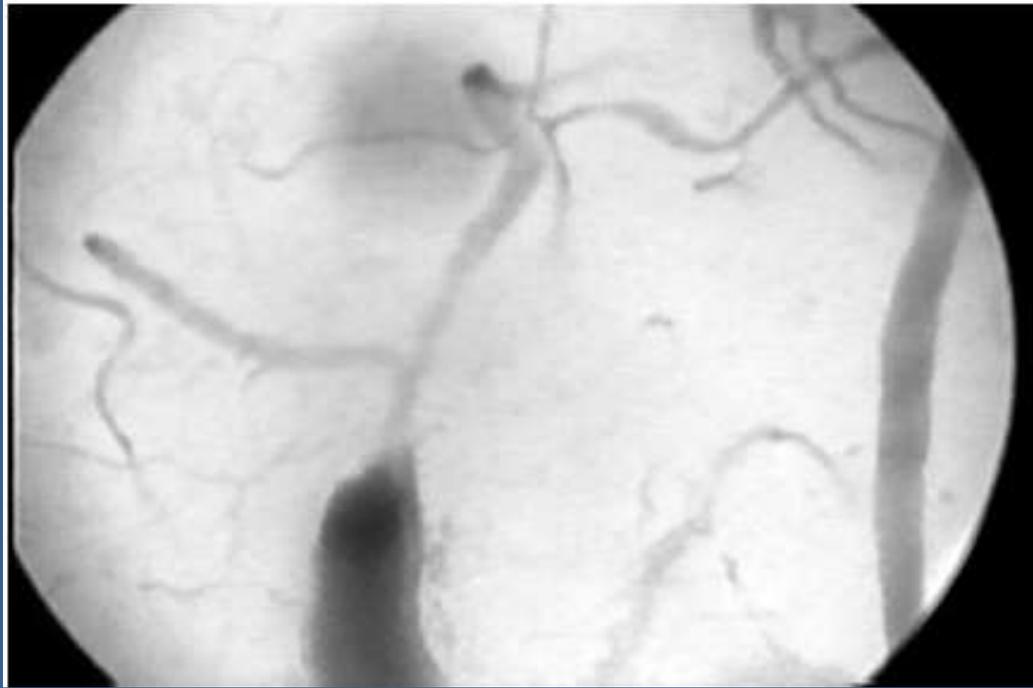
Post Resuscitation



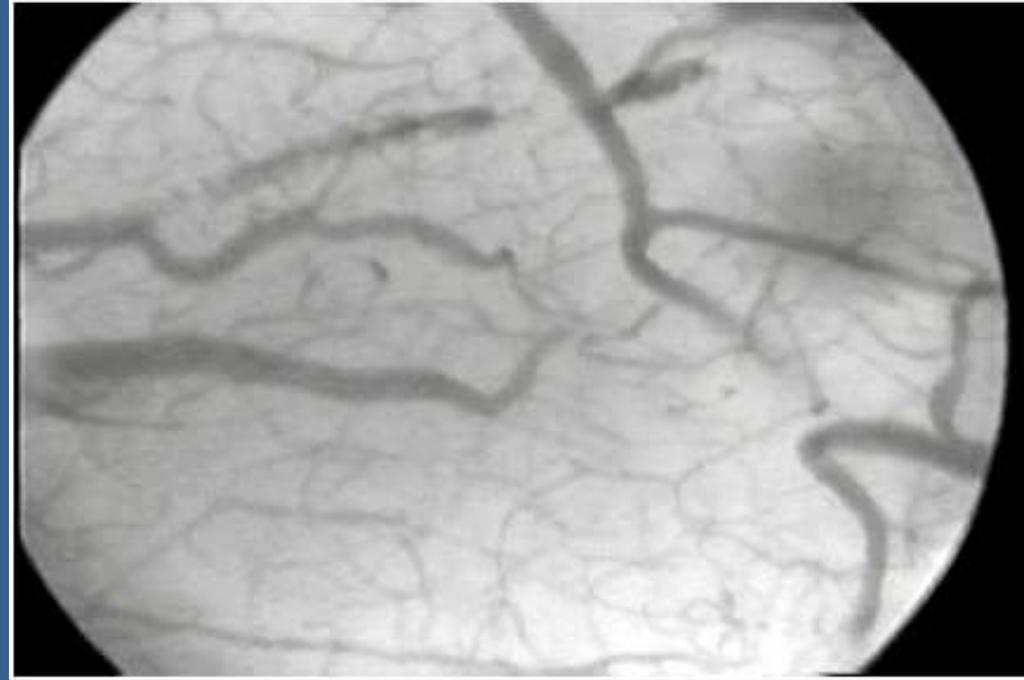
PR 7 min

Epinephrine

Post Resuscitation

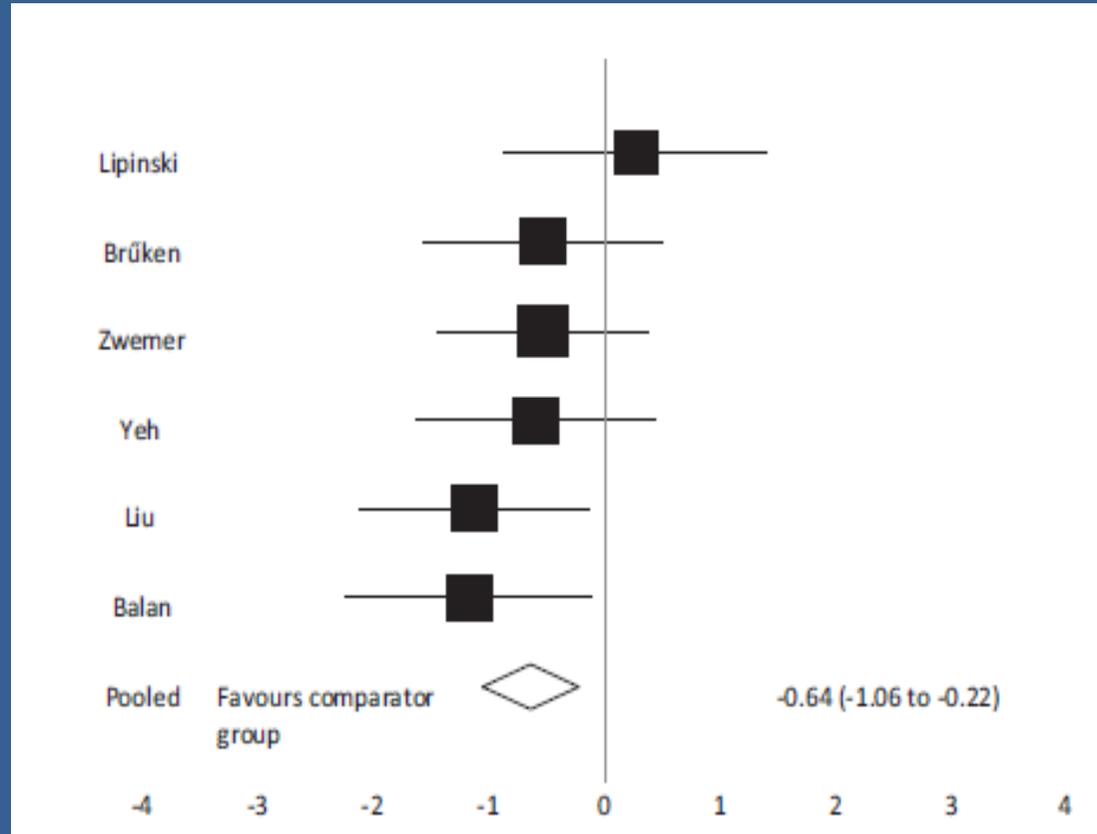


Epinephrine



Vasopressin

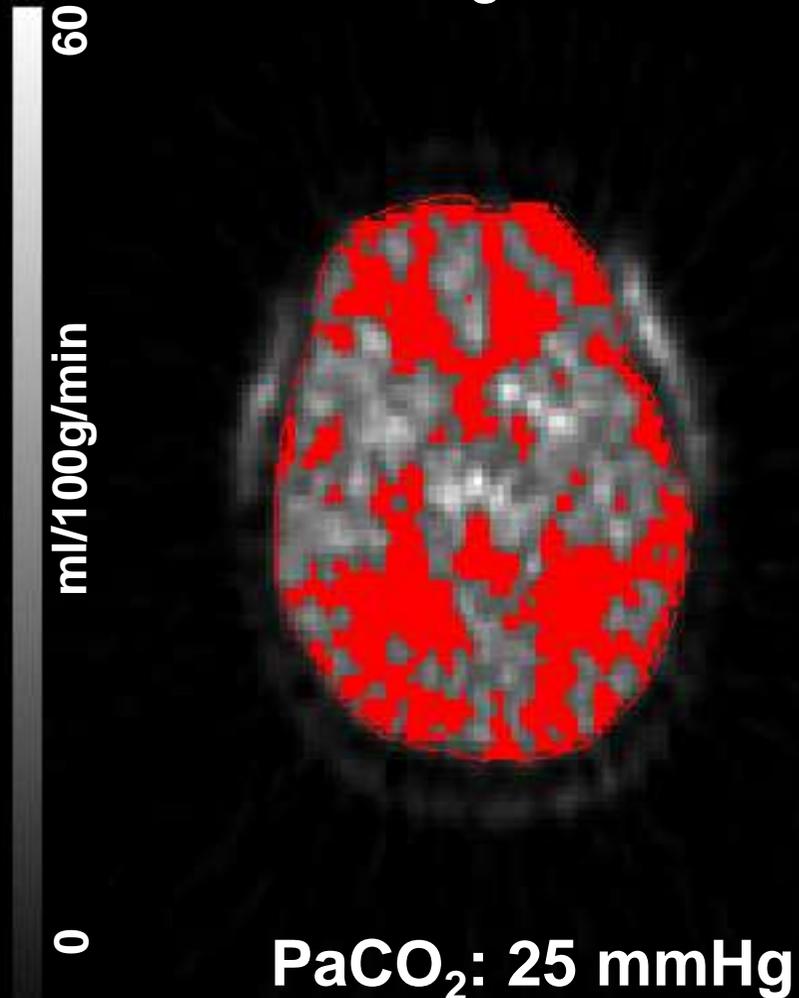
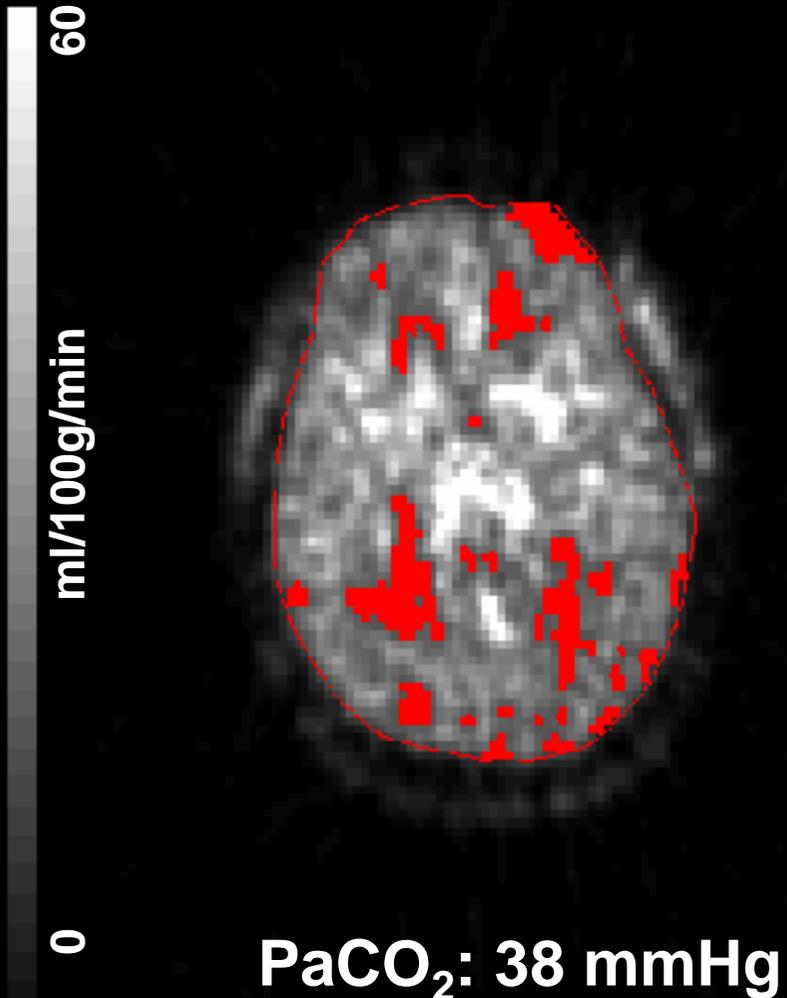
Avoid Hyperoxia



Hyperoxia and Neurological Deficit

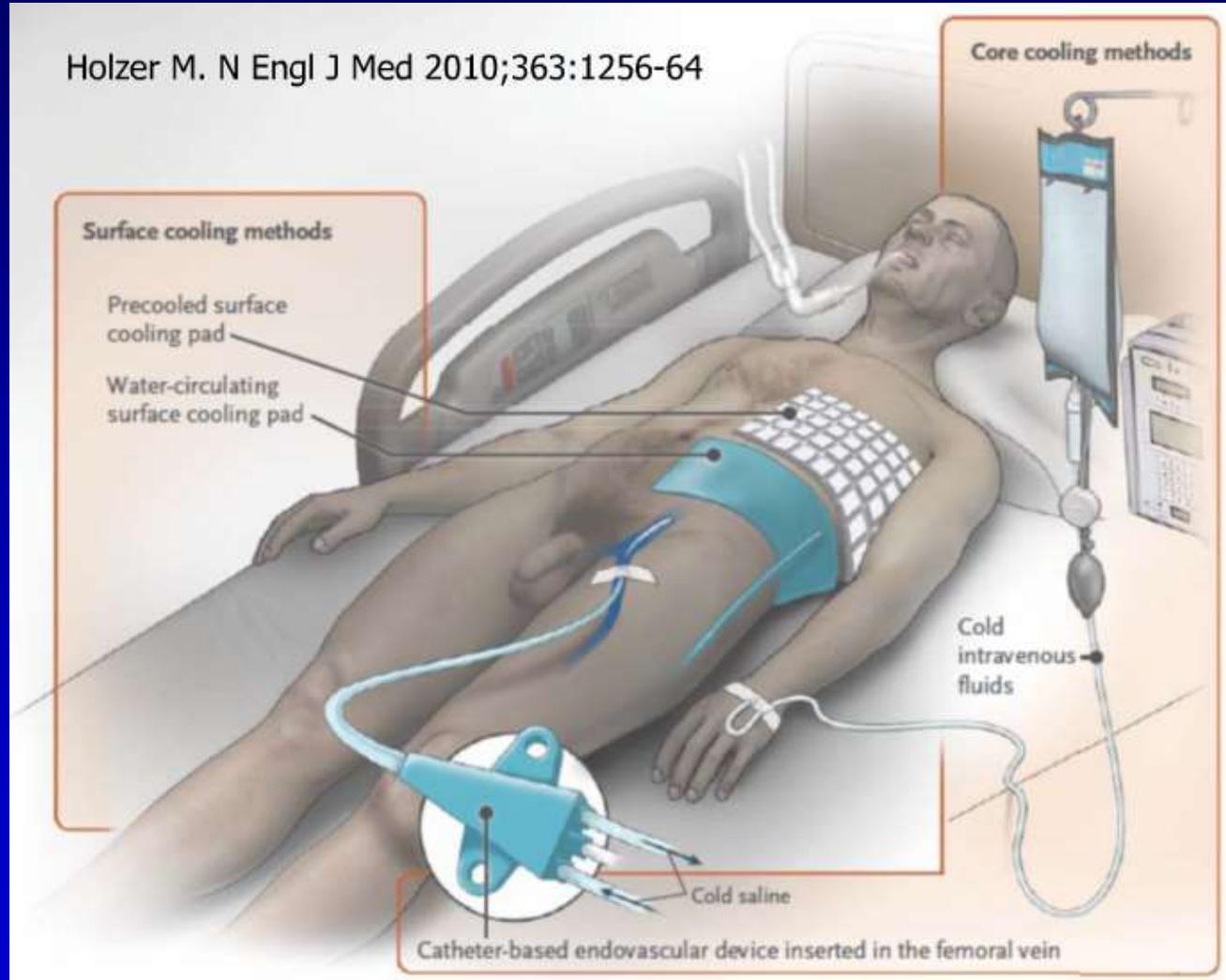
TBI (6 h after impact)

In red areas with $rCBF \leq 20$ ml/100g/min

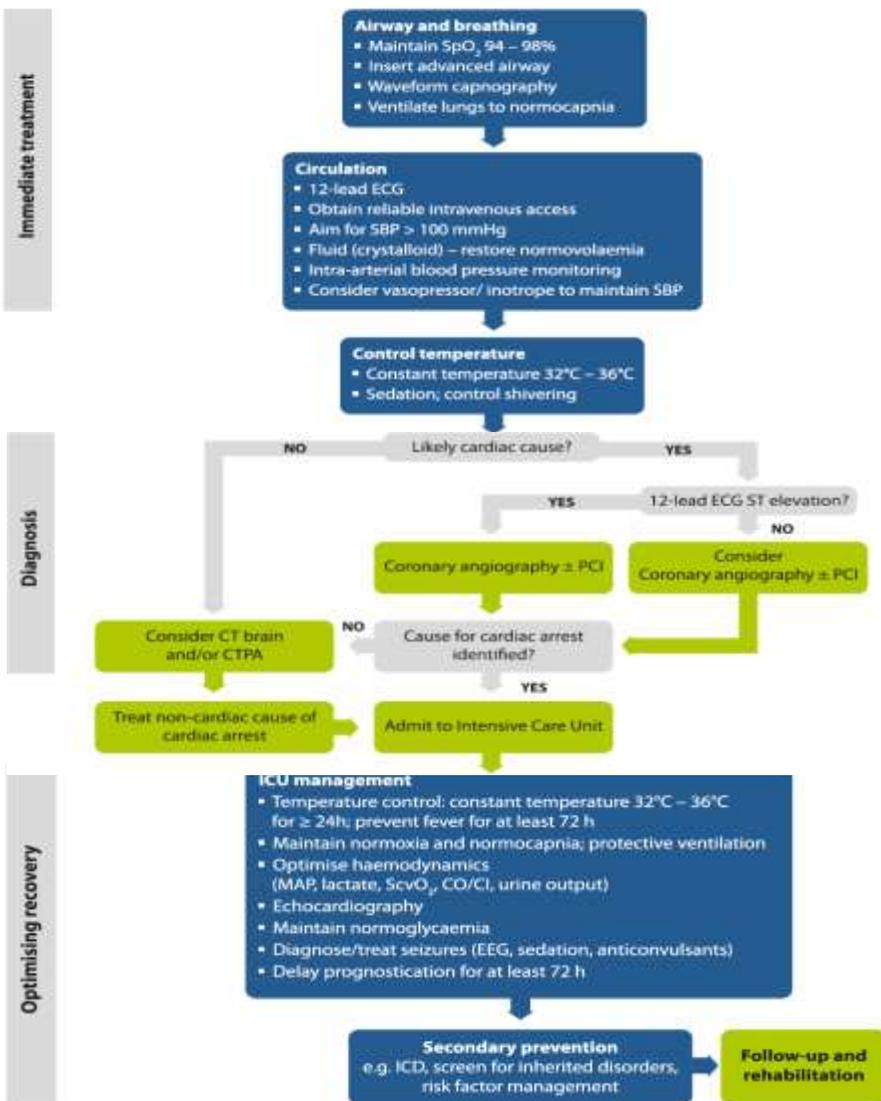


Metodi e Device

Holzer M. N Engl J Med 2010;363:1256-64



Return of spontaneous circulation and comatose



Algoritmo post- rianimazione 2015



Grazie

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2016



Italian
Resuscitation
Council