Ομάδα Εργασίας Καρδιοπνευμονικής Αναζωογόνησης

Θεσσαλονίκη 18/2/2010

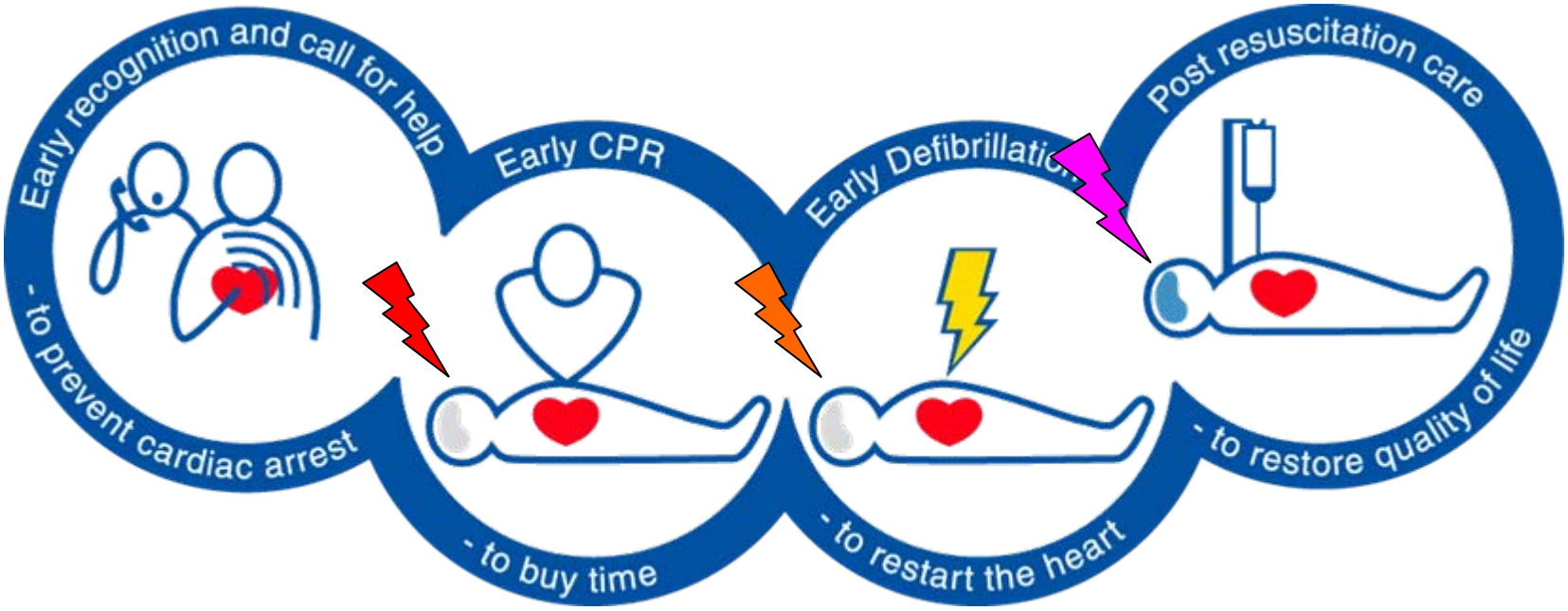
Η ΠΡΟΣΤΑΣΙΑ ΤΟΥ ΕΓΚΕΦΑΛΟΥ ΣΤΑ ΘΥΜΑΤΑ ΤΗΣ ΑΝΑΚΟΠΗΣ

Κώστας Δουλαπτσής
Β΄Καρδιολογική Κλινική
Ωνάσειο Καρδιοχειρουργικό Κέντρο

Ο ευαίσθητος εγκέφαλος...

- Μη αναστρέψιμη βλάβη αν διακοπεί η παροχή αίματος στον εγκέφαλο για 5-10 λεπτά
- Εξαιρετικά ευάλωτος στην ισχαιμία
- Ευάλωτος στις ενδεχόμενες δυσμενείς επιδράσεις της επαναιμάτωσης

BRAIN AT RISK



Ο εγκέφαλος στην καρδιακή ανακοπή

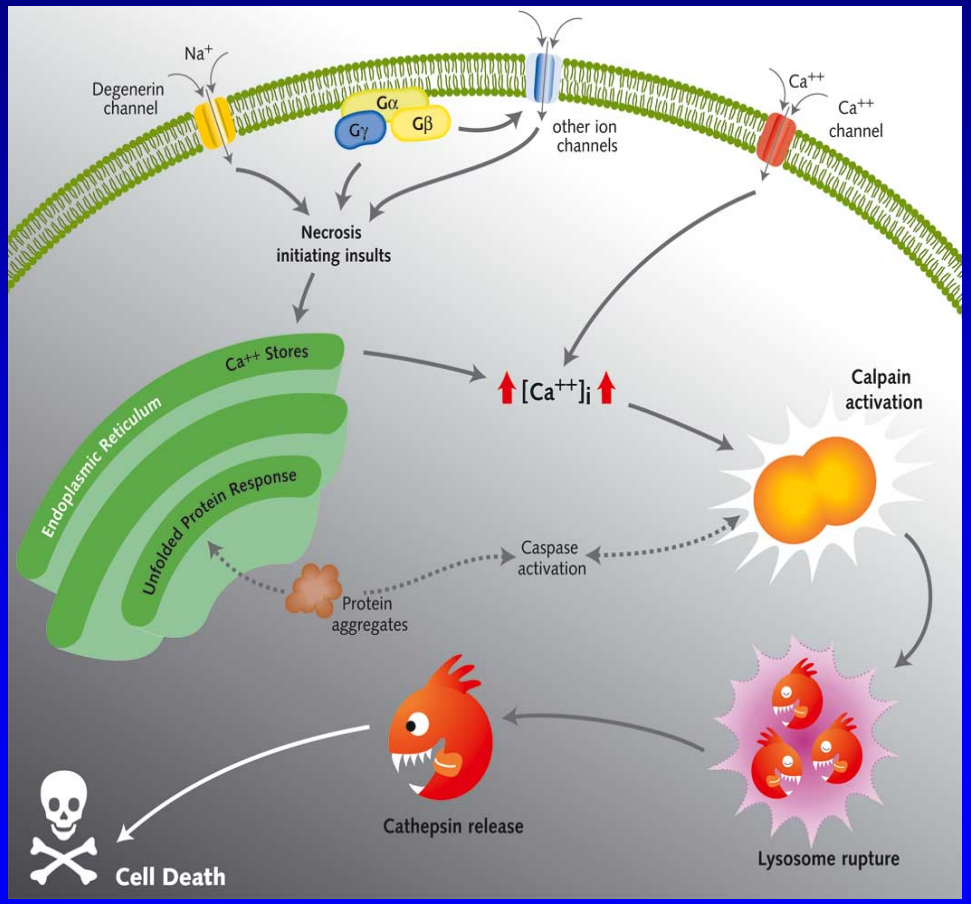
1. Διακοπή της παροχής αίματος, ανοξία και ισχαιμία των εγκεφαλικών κυττάρων (άμεσα)

2. Βλάβη επαναιμάτωσης (reperfusion injury) στη φάση ROSC

Nolan et al Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; 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; the Council on Stroke. Resuscitation 2008; 79:350-379

Μηχανισμοί εγκεφαλικής βλάβης

- Διαταραχή στην ομοιόσταση Ca^{2+}
- Απελευθέρωση ελευθέρων ριζών
- Ενεργοποίηση πρωτεασών
- Ενεργοποίηση μονοπατιών κυτταρικού θανάτου (νέκρωση & απόπτωση)

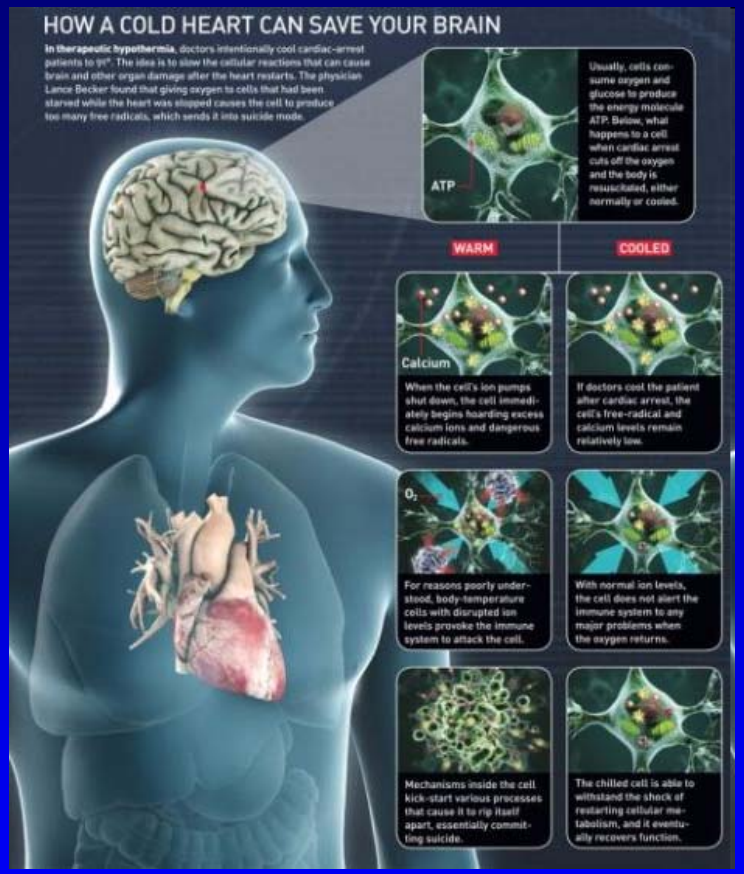


Neumar RW. **Molecular mechanisms of ischemic neuronal injury. Ann Emerg Med.** 2000;**36**:483-506.

Μηχανισμοί εγκεφαλικής βλάβης

- Εκφύλιση ευάλωτων κυτταρικών πληθυσμών σε ιππόκαμπο, φλοιό, παρεγκεφαλίδα, θάλαμο

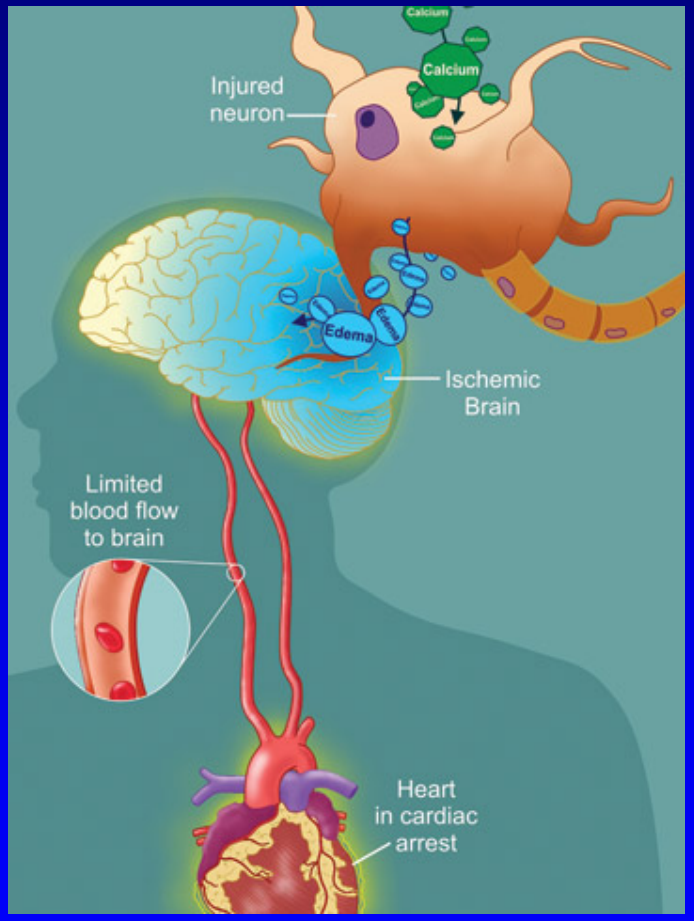
- Οι ιστολογικές και μεταβολικές διαταραχές μπορεί να διαρκούν για μέρες μετά τη ROSC



Zhang C, Siman R, Xu YA, Mills AM, Frederick JR, Neumar RW. Comparison of calpain and caspase activities in the adult rat brain after transient forebrain ischemia. Neurobiol Dis. 2002
Lipton P. Ischemic cell death in brain neurons. Physiol Rev. 1999;79:1431–1568
Blomgren K, Zhu C, Hallin U, Hagberg H. Mitochondria and ischemic reperfusion damage in the adult and in the developing brain. Biochem Biophys Res Commun. 2003;304:551–559.

Μηχανισμοί εγκεφαλικής βλάβης

- Υπεραιμία στα πρώτα λεπτά μετά τη ROSC→ εγκεφαλικό οίδημα
- Απώλεια της αυτορύθμισης της εγκεφαλικής αιματικής ροής
- Υποάρδευση και διαταραχή της εγκεφαλικής μικροκυκλοφορίας
- ↑Αγγειακές αντιστάσεις, ↓$CMRO_2$
- Ισχαιμία, θρόμβωση και μικροέμφρακτα



Sundgreen C, Autoregulation of cerebral blood flow in patients resuscitated from cardiac arrest. Stroke. 2001;32:128-132.
Schaafsma A, et al Cerebral perfusion and metabolism in resuscitated patients with severe post-hypoxic encephalopathy. J Neurol Sci. 2003;210:23-30

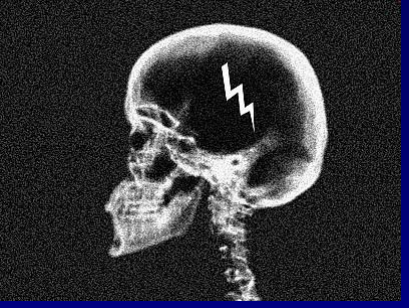
Εγκεφαλική βλάβη και..

Πυρεξία

- θ> 39^{0}C στις πρώτες 72ώρες μετά από OHCA→ αυξημένος κίνδυνος εγκεφαλικού θανάτου
- Retrospective MT: max θ> 37,8^{0}C → αυξημένη θνητότητα εντός νοσοκομείου (OR 2.7)

Ρόλος θεραπευτικής υποθερμίας

Langhelle A, et all In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. Resuscitation. 2003;56:247–263.



Εγκεφαλική βλάβη και..

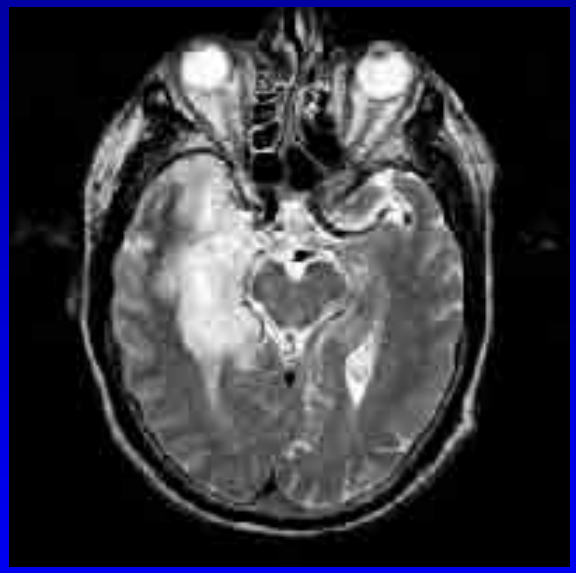
- Υπεργλυκαιμία → πτωχή πρόγνωση

- Σπασμοί → post cardiac arrest brain injury

Pulsinelli WA,et al: Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. Neurology. 1982;32:1239–1246.
Krumholz A, et al: Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. Neurology. 1988;38:401–405

Post cardiac arrest brain injury

- Βασική συνιστώσα του post cardiac arrest syndrome
- Συχνή αιτία θνησιμότητας και θνητότητας μετά από καρδιακή ανακοπή
- Κλινικές εκδηλώσεις:
  κώμα, φυτική κατάσταση, νευροψυχιατρικές διαταραχές, μυοκλόνοι, σπασμοί, πυραμιδική συνδρομή



Post cardiac arrest brain injury

- 68% των θανάτων σε ΜΕΘ (OHCA) οφείλεται σε εγκεφαλική βλάβη
- 23% των θανάτων σε ΜΕΘ (IHCA) οφείλεται σε εγκεφαλική βλάβη

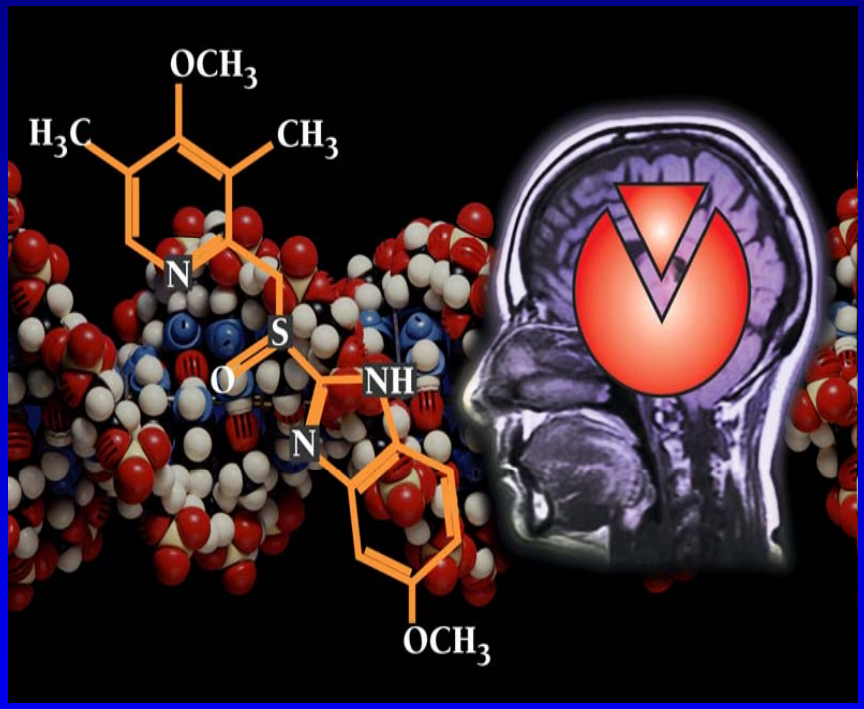
Laver S, et al Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med. 2004;30:2126-2128

There has been a considerable research into treatments that may ameliorate this neurological injury.

Hypothermia after cardiac arrest: Expanding the therapeutic scope
Bernard S, Crit Care Med 2009 Vol.37 , No. 7

Neuroprotective Pharmacology

- anesthetics
- anticonvulsants
- calcium channel antagonists (nimodipine)
- sodium channel antagonists
- N-methyl d-aspartate (NMDA)-receptor antagonists



Roine RO, et al. Nimodipine after resuscitation from out-of-hospital ventricular fibrillation. A placebo-controlled, double-blind, randomized trial. JAMA. 1990;264:3171–3177

Longstreth WT, et al. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. Neurology. 2002;59:506–514

Neuroprotective Pharmacology

- immunosuppressants
- growth factors
- protease inhibitors
- magnesium
- GABA agonists
- free-radical–trapping agents (NXY-059)
- citocholine

Lees KR, Zivin JA, Ashwood T, et al. NXY-059 for acute ischemic stroke. N Engl J Med. 2006;354:588-600
Clark WM, et al. A randomized efficacy trial of citicoline in patients with acute ischemic stroke. Stroke. 1999;30:2592-2597

Neuroprotective Pharmacology

Κανένα όφελος σε προοπτικές, τυχαιοποιημένες κλινικές μελέτες

At present the only treatment with both laboratory and clinical supportive data in this setting is therapeutic hypothermia.

Hypothermia after cardiac arrest: Expanding the therapeutic scope
Bernard S, Crit Care Med 2009 Vol.37 , No. 7

Θεραπευτική υποθερμία

- Ελεγχόμενη μείωση της θερμοκρασίας πυρήνα σώματος στους 32-34^{0}C.
- 1950's αρχικές μελέτες στη καρδιοχειρουργική και νευροχειρουργική.
- 1990's βελτίωσε τη νευρολογική έκβαση σε πειραματόζωα μετά από καρδιακή ανακοπή.

Vandam DV, Burnap TK: Hypothermia. N Engl J Med 1959; 261:546-553, 595-603

Θεραπευτική υποθερμία

- 32- 34 ^{0}C
- Ισορροπία μεταξύ κλινικού αποτελέσματος και καρδιαγγειακής τοξικότητας
- θ<31^{0}C → Slow AF
- θ<28^{0}C →VF

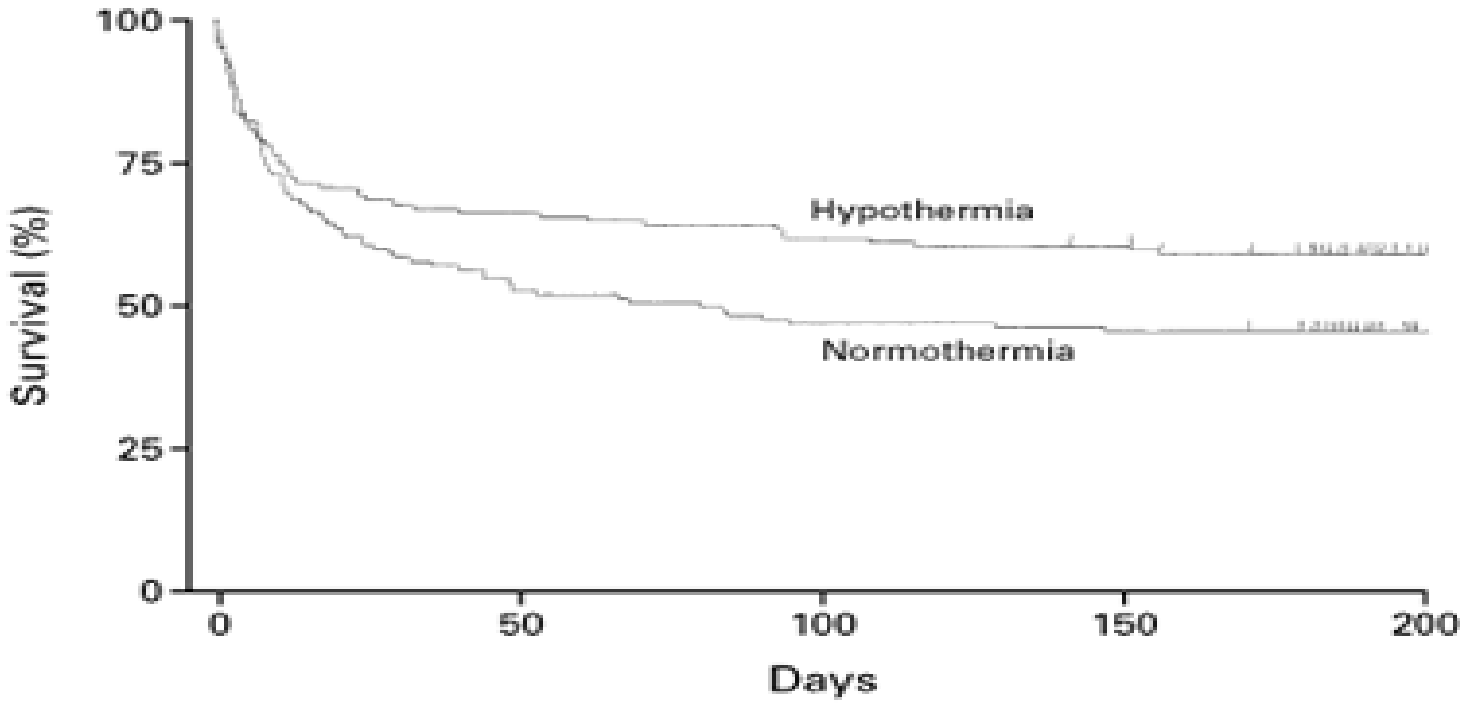
The NEW ENGLAND JOURNAL of MEDICINE

Mild Therapeutic Hypothermia to Improve the Neurologic Outcome after Cardiac Arrest

The Hypothermia after Cardiac Arrest Study Group 2002

- 9 European hospitals
- 275 pt resuscitated from cardiac arrest
- Initial cardiac rhythm is **VF**
- Hypothermia or normothermia group
- **32-34^{0}C** (air cooling blankets) for 24h
- Slow rewarming for 12 hours

The NEW ENGLAND JOURNAL of MEDICINE



No. at Risk					
Hypothermia	137	92	86	83	11
Normothermia	138	74	66	64	9

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TABLE 2. NEUROLOGIC OUTCOME AND MORTALITY AT SIX MONTHS.

OUTCOME	NORMOTHERMIA	HYPOTHERMIA	RISK RATIO (95% CI)*	P VALUE†
	no./total no. (%)			
Favorable neurologic outcome‡	54/137 (39)	75/136 (55)	1.40 (1.08–1.81)	0.009
Death	76/138 (55)	56/137 (41)	0.74 (0.58–0.95)	0.02

*The risk ratio was calculated as the rate of a favorable neurologic outcome or the rate of death in the hypothermia group divided by the rate in the normothermia group. CI denotes confidence interval.

†Two-sided P values are based on Pearson's chi-square tests.

‡A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability). One patient in the normothermia group and one in the hypothermia group were lost to neurologic follow-up.

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TABLE 4. COMPLICATIONS DURING THE FIRST SEVEN DAYS AFTER CARDIAC ARREST.*

COMPLICATION	NORMOTHERMIA	HYPOTHERMIA
	no./total no. (%)	
Bleeding of any severity†	26/138 (19)	35/135 (26)
Need for platelet transfusion	0/138	2/135 (1)
Pneumonia	40/137 (29)	50/135 (37)
Sepsis	9/138 (7)	17/135 (13)
Pancreatitis	2/138 (1)	1/135 (1)
Renal failure	14/138 (10)	13/135 (10)
Hemodialysis	6/138 (4)	6/135 (4)
Pulmonary edema	5/133 (4)	9/136 (7)
Seizures	11/133 (8)	10/136 (7)
Lethal or long-lasting arrhythmia	44/138 (32)	49/135 (36)
Pressure sores	0/133	0/136

*None of the comparisons between the two groups, performed with the use of Pearson's chi-square test, indicated significant differences.

†The sites of bleeding were mucous membranes, the nose, the urinary tract, the gastrointestinal tract, subcutaneous tissue, and skin, as well as intracerebral and intraabdominal sites.

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Exclusion criteria:

1. Rhythm other than VF
2. >75 years
3. Hypotension (MAP <60mmHg for>15min after ROSC)
4. Hypoxia (SaO2<85% for >15min after ROSC)

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia

Stephen A. Bernard, M.B., B.S., Timothy W. Gray, Michael D. Buist, Bruce M. Jones, William Silvester, Geoff Gutteridge, and Karen Smith

- 4 hospitals in Victoria
- 77 pts resuscitated from cardiac arrest
- Initial cardiac rhythm is **VF**
- Hypothermia or normothermia group
- 33^0C for 12hours
- Primary outcome: discharge at home or rehab. facility

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TABLE 5. OUTCOME OF PATIENTS AT DISCHARGE FROM THE HOSPITAL.

OUTCOME*	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)
	number of patients	
Normal or minimal disability (able to care for self, discharged directly to home)	15	7
Moderate disability (discharged to a rehabilitation facility)	6	2
Severe disability, awake but completely dependent (discharged to a long-term nursing facility)	0	1
Severe disability, unconscious (discharged to a long-term nursing facility)	0	1
Death	22	23

*The difference between the rates of a good outcome (normal or with minimal or moderate disability) in the hypothermia and the normothermia groups (49 percent and 26 percent, respectively) was 23 percentage points (95 percent confidence interval, 13 to 43 percentage points; P=0.046). The unadjusted odds ratio for a good outcome in the hypothermia group as compared with the normothermia group was 2.65 (95 percent confidence interval, 1.02 to 6.88; P=0.046). The odds ratio for a good outcome in the hypothermia group as compared with the normothermia group, after adjustment by logistic regression for age and time from collapse to return of spontaneous circulation, was 5.25 (95 percent confidence interval, 1.47 to 18.76; P=0.011).

Exclusion criteria:

1. Rhythm other than VF
2. Hypotension (MAP <60mmHg for>15min after ROSC)

Older and hypoxic patients were included

- *Unconscious adult patients with ROSC after OHCA arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was **VF** (Class IIa).*

- *Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb).*

Hypothermia and non-VF rhythm

- Η πλειονότητα των ασθενών με *OHCA δεν* παρουσιάζει *VF (PEA & Asystole)*
- Οι ασθενείς με ασυστολία πιθανά έχουν παρατεταμένη καρδιακή ανακοπή→ σοβαρή νευρολογική βλάβη →χαμηλότερη επιβίωση
- Επιζεί μόνο 7-12% των ασθενών σε υποθερμία και non VF arrest

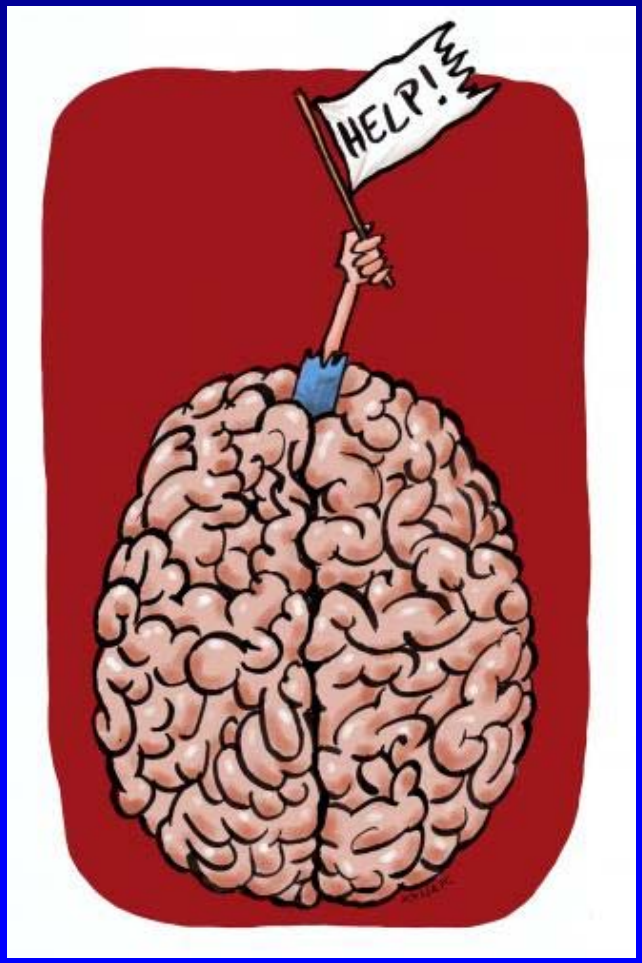
Kim F, et al.Pilot Randomized Clinical Trial of Prehospital Induction of Mild Hypothermia in Out-of-Hospital Cardiac Arrest Patients With a Rapid Infusion of 4°C Normal Saline

Critical Care Medicine

Hypothermia after cardiac arrest: Expanding the therapeutic scope

Bernard, Stephen MD

It is unlikely that clinical trials will be undertaken to test the efficacy of therapeutic hypothermia in ***non VF arrest*** *because of the very large sample size that would be required to detect a significant difference in outcomes*.



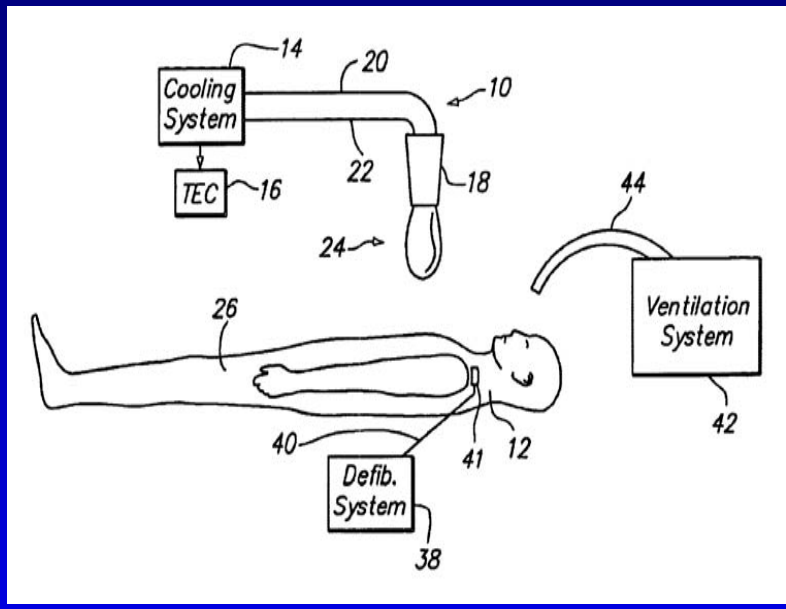
Τα 4 στάδια της θεραπευτικής υποθερμίας

1. Εισαγωγή
2. Διατήρηση
3. Επαναθέρμανση
4. Νορμοθερμία

Εισαγωγή (Induction)

Μετά από:

- την αρχική νευρολογική εκτίμηση
- την τοποθέτηση **θερμομέτρου** (οισοφάγο, πνευμονική αρτηρία, ουροδόχο κύστη) για συνεχή μέτρηση θερμοκρασία πυρήνα σώματος με δυνατότητα ανάδρασης (feedback).
- την χορήγηση καταστολής (μιδαζολάμης) & νευρομυϊκού αποκλεισμού (vecuronium)



N. Kupchik Development and implamentation of a therapeutic hypothermia protocol Crit Care Med 2009 Vo 37

Εισαγωγή (Induction)

- Υπάρχει ήδη υποθερμία μετά την ROSC
- Πάγος
- Κουβέρτες ψύχους
- Water circulating pads
- Τέντα με ψυχρό αέρα

D. seder, Methods of cooling: practical aspects of therapeutic temperature management Crit Care Med2009 Vol 37

Εισαγωγή (Induction)

- Ενδοφλέβια ταχεία χορήγηση 30-40ml/kg κρύου (4^0C) ισοτονικού υγρού ακόμη και προνοσοκομειακά
- Μείωση θερμοκρασίας πυρήνα κατά $1,6^0$C.
- Βελτιώνει την οξεοβασική ισορροπία.
- Δεν αύξησε την επίπτωση του πνευμονικού οιδήματος.

Francis Kim, MD; et al Pilot Study of Rapid Infusion of 2 L of 4°C Normal Saline for Induction of Mild Hypothermia in Hospitalized, Comatose Survivors of Out-of-Hospital Cardiac Arrest *Circulation* 2005; 112;715-719

Εισαγωγή (Induction)

External cooling

- Rapid cooling
- Only for induction
- 37min ☞ < 34^0C

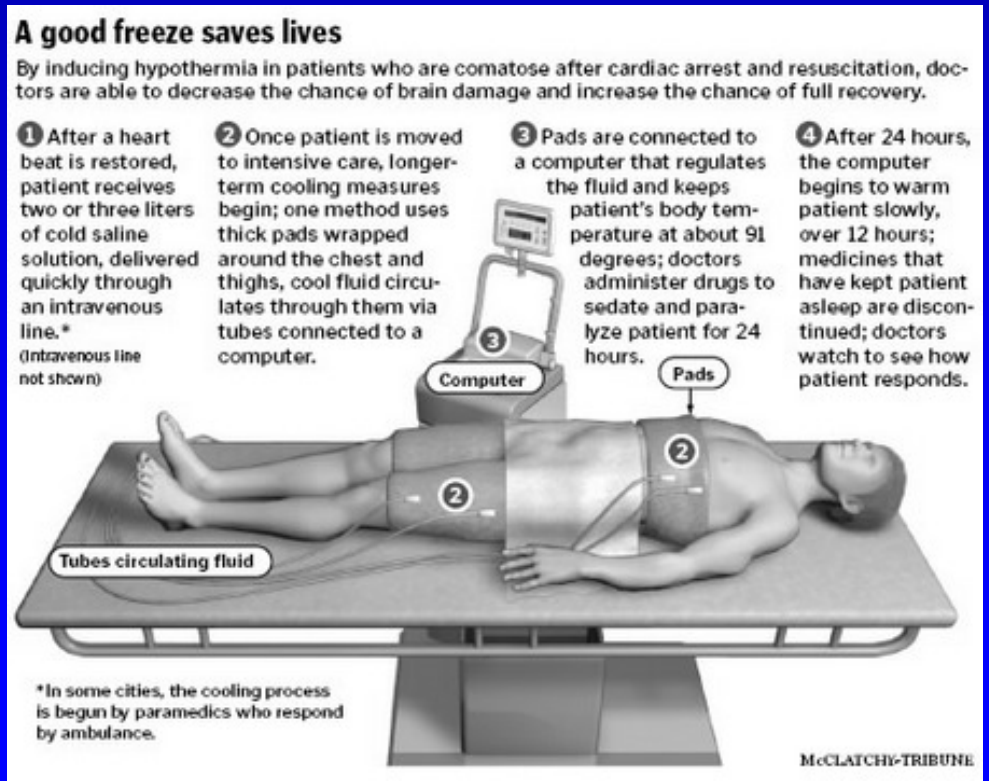
Rapid induction of therapeutic hypothermia using convective-immersion surface cooling: Safety, efficacy and outcomes *Resuscitation 2009*

Διατήρηση (maintenance)

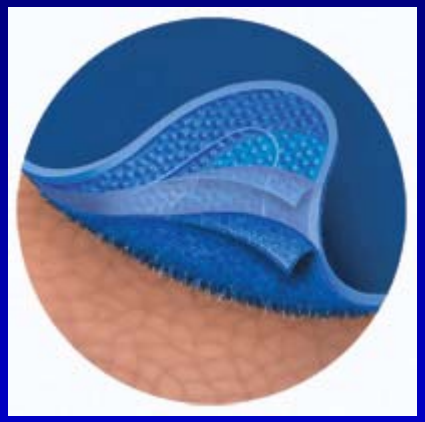
External cooling

- cooling blankets

•pads with water-filled circulating systems



Διατήρηση (maintenance)



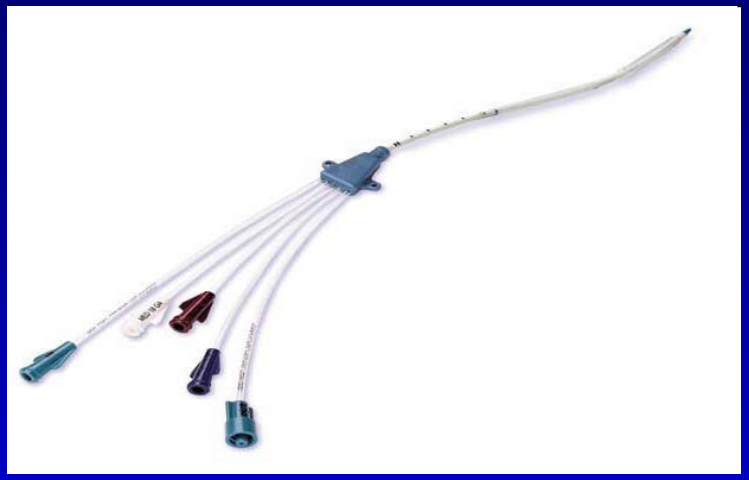
External cooling

- Pads with hydrophilic gel
- 40% surface area
- Expensive
- skin complications

D. seder, Methods of cooling: practical aspects of therapeutic temperature management Crit Care Med2009 Vol 37

Διατήρηση (maintenance)

Internal cooling devices:



- Intravascular cooling catheters are inserted into a femoral or subclavian vein
- Accurate but expensive
- Requires physician

Schmutzhard, E. et al Safety and efficacy of a novel intravascular cooling device to control body temperature in neurologic intensive care patients Crit Care Med 2002; 30:2481-2488

Διατήρηση (maintenance)

- Avoid ice packs and wet cold blankets:
  → over- or undercooling
  → time consuming for nursing staff

- Avoid cold IV fluids alone

- *Internal* or *external cooling* devices with continuous temperature feedback to achieve a target temperature

Επαναθέρμανση (rewarming)

- The rewarming phase can be regulated using the external or internal devices used for cooling

- The optimal rate of rewarming is not known, but current consensus is to rewarm at about 0.25–0.5 °C/h

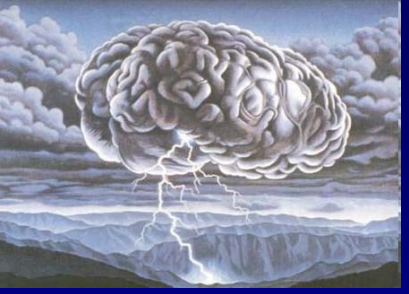
Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med. 2007;35:1041–1047

Νορμοθερμία (normothermia)

- Διατήρηση νορμοθερμίας **(36,5- 37,5^{0}C)**
- “Rebound fever”→ επιβλαβής και αντιμετωπίζεται με κάποια από τις συσκευές ψύχους που χρησιμοποιήθηκαν για υποθερμία
- Απαιτεί νοσηλευτική εγρήγορση

Επιπλοκές της υποθερμίας

- Ρίγος
- Αρρυθμίες (βραδυκαρδία)
- Υπεργλυκαιμία (↓ευαισθησίας σε ινσουλίνη)
- Αιμορραγίες (επίδραση στην πήξη και στα αιμοπετάλια)
- Λοιμώξεις-πνευμονία (ανοσοκαταστολή)



Επιπλοκές από την υποθερμία

- ↑ SVR & ↓CO
- ↑διούρηση, υπογκαιμία, αιμοδυναμική αστάθεια
- Ηλεκτρολυτικές διαταραχές (↓ K, Ca, Mg, P)
- ↓ clearance (τροποποίηση των φαρμακευτικών δόσεων)

Προστασία του εγκεφάλου- Monitoring

- Intensive care monitoring
- Advanced haemodynamic monitoring
- Continuous core temperature measurements
- Cerebral monitoring

EEG monitoring in TH

- Επίπτωση σπασμών σε καρδιακή ανακοπή (19-34%)
- Αδύνατη η αναγνώριση σπασμών λόγω μυοχάλασης
- Εναλλακτικά μπορεί να γίνει καταστολή με αντιεπιληπτικά φάρμακα.

Classen et al: Dtection of seizures with continous EEG monitoring in critically ill patients. *Neurology* 2004; 62:1743-1748

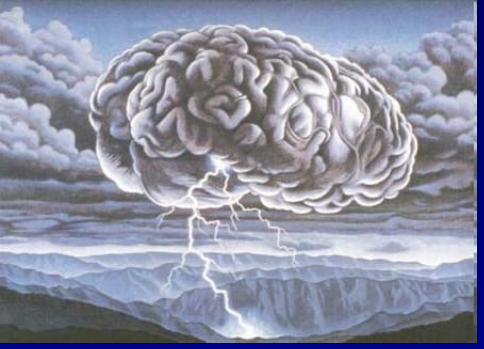
Oxygenation- Ventilation

- Not hypoxemic
- Hyperoxia (100% O_2) during the early stages harms postischaemic neurons (excessive oxidative stress)
- Preclinical evidence shows that unnecessary arterial hyperoxia should be avoided, especially during the initial post-cardiac arrest period (FiO_2 94–96%)
- Hyperventilation should be avoided in the post-cardiac arrest period.
- Ventilation should be adjusted to achieve normocarbia

Richards EM, et al : Hyperoxic reperfusion after global ischemia decreases hippocampal energy metabolism. Stroke. 2007;38:1578–1584
Zwemer CF, et al: Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs. Resuscitation. 1994;27:159–170

Haemodynamics

- CVP=8-12 mmHg
- 3,5-6 lt of crystaloid fluids may be required in the first 24h
- MAP= 65-90 mmHg
- Use inotropes, vasopressors if necessary



Νευρο-προγνωστικές μέθοδοι

- Νευρολογική εκτίμηση (GCS, αντανακλαστικά στελέχους, CPC)
- Νευροφυσικές δοκιμασίες (somatosensory-evoked potentials (SSEP)
- Απεικόνιση (CT, MRI, PET)
- Βιοχημικοί δείκτες (neuron-specific enolase [NSE] & S100β

Functional outcome

The Cerebral Performance Category (CPC) score [49] is the most commonly used instrument to assess functional outcome after cardiac arrest; its categories are:

1. Conscious and alert with good cerebral performance; able to work and lead a normal life; may have minor neurological deficits
2. Conscious with moderate cerebral disability; independent for activities of daily life; sufficient cerebral function for part-time work in sheltered environment; may have seizures or permanent memory or mental changes
3. Conscious with severe disability; dependent on others for activities of daily life because of impaired brain function
4. Not conscious (comatose or persistent vegetative state)
5. Brain dead or death from other causes

Sandroni Intensive Care Med 2007;33: 237

SUPPORT Study FitzGerald Arch Intern Med 1997;157: 72

- *Hypothermia may mask neurological examination or delay the clearance of medication, such as sedative or neuromuscular blocking drugs.*

Wijdicks EF. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2006;67:203-210

Resuscitation (2007) 75, 219–228

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REVIEW PAPER

Biochemical markers (NSE, S-100, IL-8) as predictors of neurological outcome in patients after cardiac arrest and return of spontaneous circulation☆

Konstantinos A. Ekmektzoglou, Theodoros Xanthos*, Lila Papadimitriou

Biochemical markers for prediction of neurological outcome after cardiac arrest.

NSE S-100 Il-8

Greece **Ekmektzoglou Resuscitation 2007;75: 219**

Επηρεάζει η υποθερμία την εγκυρότητα των συνηθισμένων μεθόδων εκτίμησης της πρόγνωσης;

- 48-h NSE and S100 values which achieved a 0% FPR for poor outcome were 2–3 times higher in patients treated with hypothermia compared with the normothermic control group [NSE > 25 versus 8.8 μg L−1; S100β 0.23 versus 0.12 μg L−1].

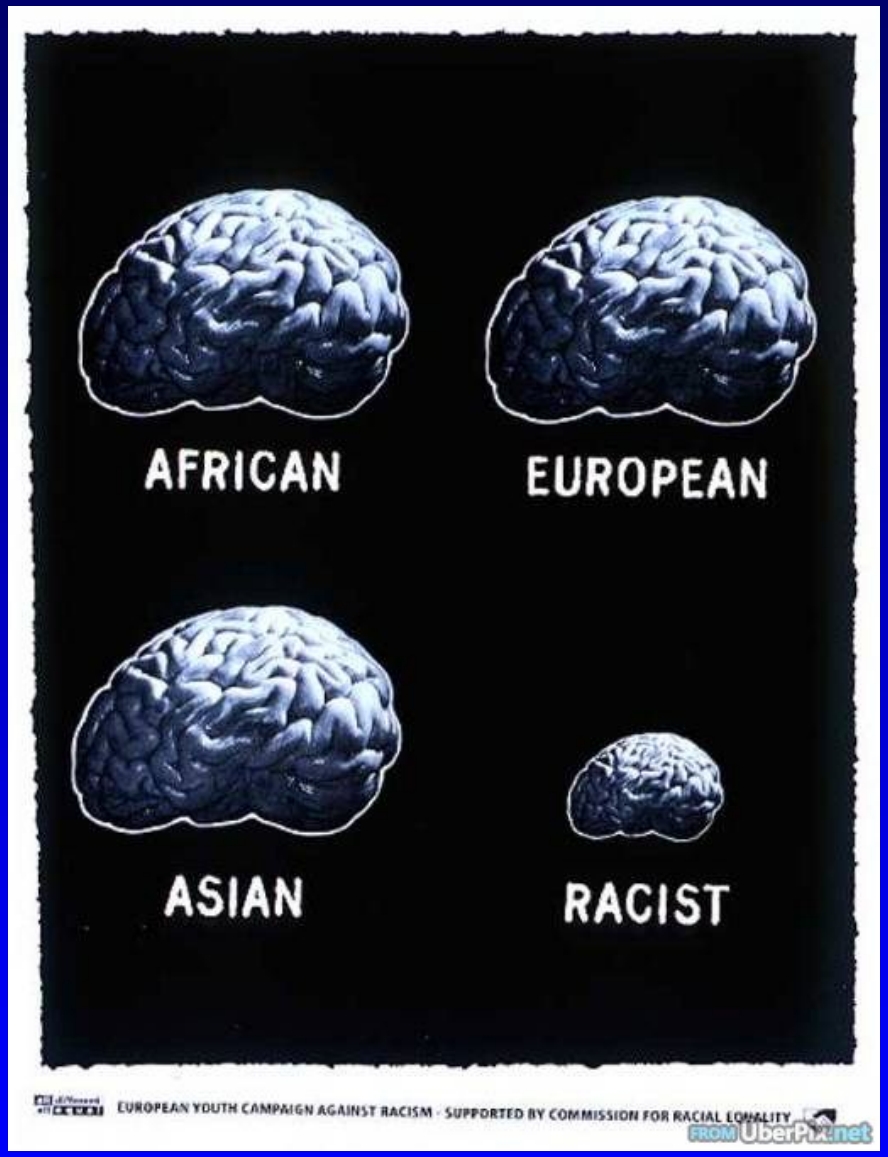
Tiainen. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. *Stroke.* 2003;34:2881-2886.

Επηρεάζει η υποθερμία την εγκυρότητα των συνηθισμένων μεθόδων εκτίμησης της πρόγνωσης;

- *When cardiac arrest patients are treated with therapeutic hypothermia prognostication should probably be delayed, but the optimal time has yet to be determined.*

Nolan et al Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; 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; the Council on Stroke. Resuscitation 2008; 79:350-379

- TH is the only current treatment to ameliorate brain injury after CA
- TH for VF arrest
- TH for non VF arrest (balance benefit & feasibility)
- Team and team spirit
- New surface and intravascular cooling techniques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