idcsalud
Hospital Universitari Sagrat Cor

CONTROVÈRSIES EN HIPOTÈRMIA
EL "PRO"
Congrés SOCMIC 2015

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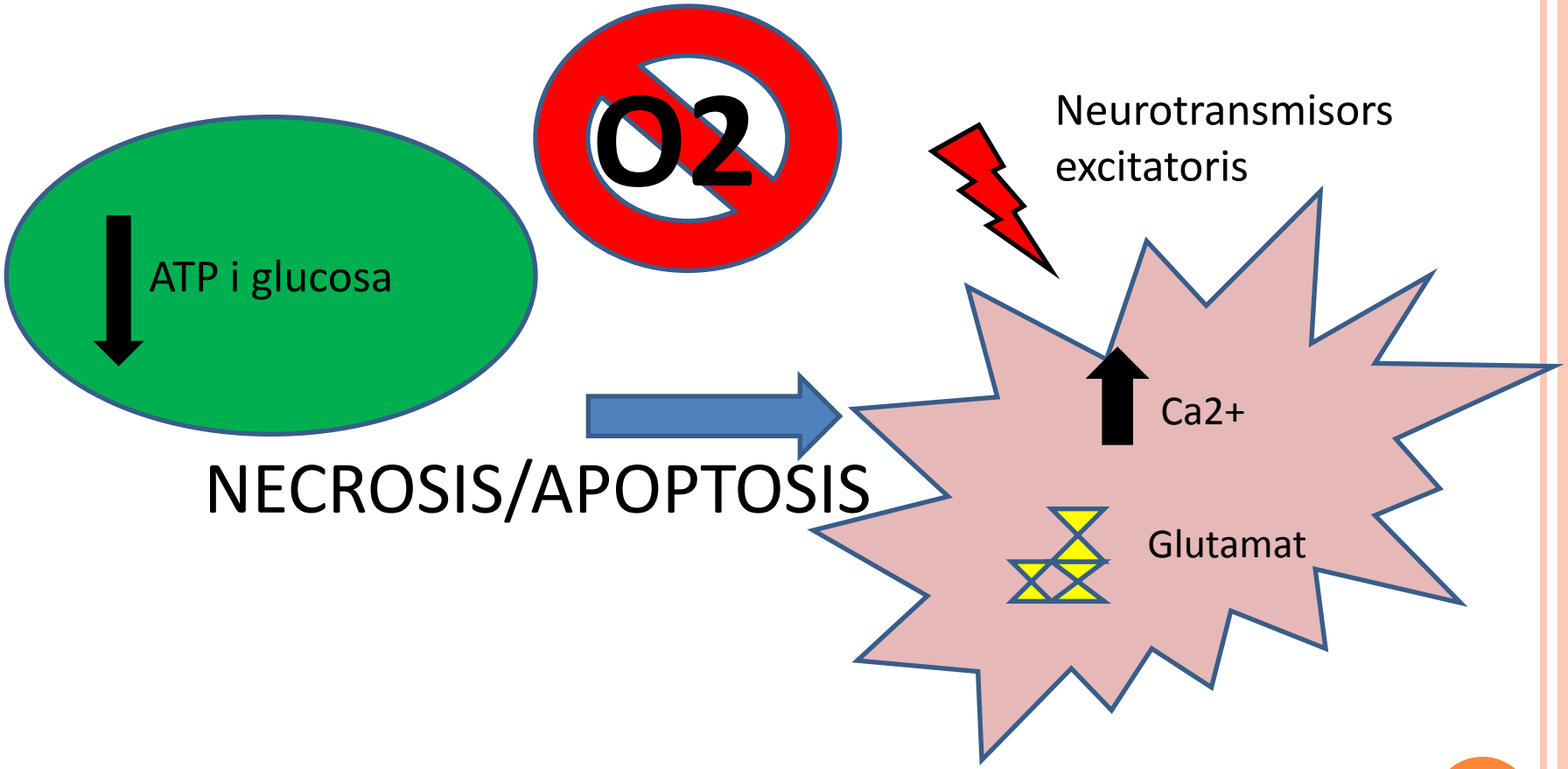
5 de Març 2015

Anòxia cerebral



Lesió de reperfusió

O2

↓

cascada inflamatòria + radicals lliures

↓

↑ disfunció endotelial i augment de l'edema

↓

augmenta el dany neurològic

Paper de la hipotèrmia

- Modera la cascada inflamatòria→ ⇓ l'alliberació d'aminoàcids excitatoris i els radicals lliures.

- ⇓ la taxa metabòlica cerebral d´O2, el volum de sang cerebral, la PIC.
- Millora el desajust entre l'oferta i la demanda d'oxigen.

Clinical Trial of Induced Hypothermia in Comatose Survivors of Out-of-Hospital Cardiac Arrest

Stephen A Bernard, MB BS*
Bruce MacC Jones, MB BS*
Malcolm K Horne, BMedSci, MB BS, PhD†

Ann Emerg Med 1997;30:146-53

· Objectiu: efectes de HT moderada en pc post-ACR extra-hospitalària.

·Estudi prospectiu del grup amb HT moderada (22 pc 1993-1996) amb control retrospectiu (22 pc 1991-1993).

Resultats

Table 4.

*GOCS scores at hospital discharge.**

GCS Category	Hypothermic (n=22)	Normothermic (n=22)
1: Normal/minimal disability	8	2
2: Moderate disability	3	1
3: Conscious, severe disability	1	1
4: Vegetative state	0	1
5: Dead	10	17

*Differences between the two groups were significant for categories 1 and 2 (11 versus 3; $P < .05$) and category 5 (10 versus 17; $P < .05$).

No hi va haver diferències significatives en quant a efectes adversos induïts per la hipotèrmia.

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, 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.

· Estudi prospectiu i randomitzat. Entre l'any 1996-1999.

.Criteris d'inclusió: AC extra-hospitalària ; FV com a ritme inicial , recuperació de la circulació espontánea i coma post-recuperació de la circulació espontánea.

·Grup d'hipotèrmia moderada (T 33ºC) durant 12h amb normotèrmia (37ºC)

· Objectiu primari: mesurar la supervivència a l'alta hospitalària amb bon estat neurològic.

·Objectiu secundari: efectes hemodinàmics, bioquímics i hematològics de la hipotèrmia.

TABLE 1. CLINICAL CHARACTERISTICS OF THE 77 PATIENTS WITH ANOXIC BRAIN INJURY WHO WERE ELIGIBLE FOR RANDOMIZATION.*

CHARACTERISTIC	HYPOTHERMIA (N=43)	NORMOTHERMIA (N=34)	P VALUE
Age (yr)			0.55
Median	66.8	65.0	
Range	49–89	41–85	
Male sex (%)	58	79	0.05
Arrest witnessed (%)	95	94	0.81
Bystander performed cardiopulmonary resuscitation (%)	49	71	0.05
Time from collapse to emergency-medical-services call (min)	2.1±1.9	2.7±3.0	0.32
Time from call to emergency-medical-services arrival (min)	7.9±3.1	8.3±2.8	0.60
Time from arrival to first DC shock (min)	2.5±2.2	2.0±1.2	0.22
Time from first shock to return of spontaneous circulation (min)	13.6±11.2	12.1±7.9	0.48
Time from collapse to return of spontaneous circulation (min)	26.5±12.9	25.0±8.9	0.54
Number of DC shocks	4.2±3.0	4.1±3.2	0.87
Dose of epinephrine (mg)	2.2±2.1	2.2±1.9	0.97

*Plus–minus values are means ±SD. DC denotes direct current.

Pronòstic neurològic

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).

Taxa bon pronòstic neurològic HT vs NT: 46% vs 26%. IC 95%; p=0,046

Efectes bioquímics de la HT

TABLE 3. BIOCHEMICAL VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ED	ADMISSION TO ICU	6 Hr	12 Hr	18 Hr	24 Hr
Number of patients	Hypothermia	43	39	39	39	39	38
	Normothermia	34	33	32	32	32	31
Potassium (mmol/liter)	Hypothermia	3.8 (2.5–7.8)	3.6 (2.6–6.9)	3.6 (2.7–6.3)	4.1 (2.6–7.6)	4.3 (3.1–5.6)†	4.5 (2.9–7.1)‡
	Normothermia	3.9 (2.2–6.4)	3.9 (2.5–5.1)	4.0 (2.7–5.7)	4.2 (3.3–5.7)	4.1 (3.1–6.0)	3.9 (3.9–4.6)
	P value§	0.84	0.98	0.06	0.52	0.05	<0.001
Lactate (mmol/liter)	Hypothermia	8.3 (2.2–14.9)	2.7 (0.9–11.6)‡	3.7 (1.2–11.8)‡	4.4 (1–11.1)‡	3.4 (0.5–10.3)‡	2.5 (0.7–11.4)‡
	Normothermia	7.5 (2–14)	2.6 (0.9–8.4)‡	3.3 (1.1–9.3)‡	3.5 (1–12.4)‡	2.6 (0.7–11)‡	1.6 (0.6–11)‡
	P value§	0.75	0.46	0.79	0.67	0.18	0.08
Glucose (mmol/liter)¶	Hypothermia	13.3 (9.0–33.0)	16.2 (7.4–26.8)	16.0 (7.1–36.7)	16.1 (4.2–28)	10.5 (4.2–25)‡	8.0 (1.6–27.8)‡
	Normothermia	12.6 (4.8–22.7)	10.5 (6.6–17.9)	12.1 (5.8–25)	11.6 (6.2–28)	10.7 (5.3–21)	7.5 (3.5–15.1)‡
	P value§	0.13	0.002	0.02	0.14	0.97	0.92
Creatine kinase (mmol/liter)	Hypothermia	149 (25–3295)	261 (85–3061)‡	635 (95–6068)‡	1544 (110–9795)‡	2221 (95–7590)‡	1079 (85–8670)‡
	Normothermia	111 (67–635)	525 (69–2949)‡	651 (79–5306)‡	1205 (90–5750)‡	1295 (85–6794)‡	1274 (95–11,061)‡
	P value§	0.32	0.99	0.72	0.76	0.93	0.49
Creatine kinase MB (mmol/liter)	Hypothermia	21 (4–120)	27 (8–133)	50 (5–247)†	39 (5–559)‡	66 (5–432)‡	57 (4–321)‡
	Normothermia	21 (10–117)	40 (5–224)	27 (5–259)	31 (5–875)	25 (5–190)	33 (6–423)†
	P value§	0.35	0.80	0.23	0.22	0.05	0.28
Creatinine (μmol/liter)‖	Hypothermia	140 (38–211)	122 (62–215)‡	110 (50–220)‡	108 (35–345)‡	104 (35–270)‡	109 (47–310)‡
	Normothermia	125 (75–297)	120 (72–311)‡	110 (66–260)	127 (55–354)	95 (45–375)	111 (50–394)†
	P value§	0.78	0.86	0.11	0.10	0.23	0.96
Arterial pH	Hypothermia	7.29±0.11	7.35±0.11‡	7.33±0.08	7.31±0.11	7.33±0.11	7.37±0.10‡
	Normothermia	7.27±0.09	7.37±0.06‡	7.36±0.07‡	7.36±0.09‡	7.37±0.06‡	7.40±0.06‡
	P value§	0.78	0.87	0.15	0.04	0.05	0.07

*Plus–minus values are means ±SD. Medians and ranges (in parentheses) are given for other variables, which were log-transformed before analysis of variance was performed, because of nonparametric distribution. One patient in the hypothermia group and two in the normothermia group died during the first 24 hours. ED denotes emergency department, and ICU intensive care unit.

†P<0.05 for the comparison with the value on admission to the emergency department.

‡P<0.01 for the comparison with the value on admission to the emergency department.

§P values are for the differences between the hypothermia and the normothermia groups.

¶To convert the values for glucose to milligrams per deciliter, divide by 0.05551.

‖To convert the values for creatinine to milligrams per deciliter, divide by 88.4.

Efectes hematològics de la HT

TABLE 4. HEMATOLOGIC VALUES.*

VARIABLE	TREATMENT GROUP	ADMISSION TO ED	12 HR	24 HR
Number of patients	Hypothermia	43	39	38
	Normothermia	34	32	31
Platelet count ($\times 10^{-3}$/mm^3)	Hypothermia	209±65.7	193±60.2†	190±63.3†
	Normothermia	221±63.4	217±63.0	199±54.2†
	P value‡	0.46	0.24	0.82
White-cell count ($\times 10^{-3}$/mm^3)	Hypothermia	10.9 (5.7–21.5)	14.5 (5.5–30.4)§	14.6 (7.1–35.3)§
	Normothermia	11.1 (6.3–25.3)	14.6 (8.5–29)§	15.8 (9.8–25.3)§
	P value‡	0.46	0.12	0.34

The New England
Journal of Medicine

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

· Estudi multicèntric (9 centres europeus) entre Març 1996 al Gener 2001.

· Hipotèrmia moderada (32-34ºC durant 24h) vs normotèrmia.

· Objectiu principal: resultat neurològic favorable als sis mesos de la ACR mesurat amb la categoria de Cerebral Performance Catergory.

· Objectiu secundari: mortalitat als 6 mesos i la incidència de complicacions durant els primers 7 dies.

·Criteria d'inclusió: PCR presenciades; FV / TVSP, causa cardíaca, 18 a 75 anys, entre 5-15 min des de la PCR a les primeres maniobre i < 60min des de la PCR a ROSC.

Objectiu primari

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.

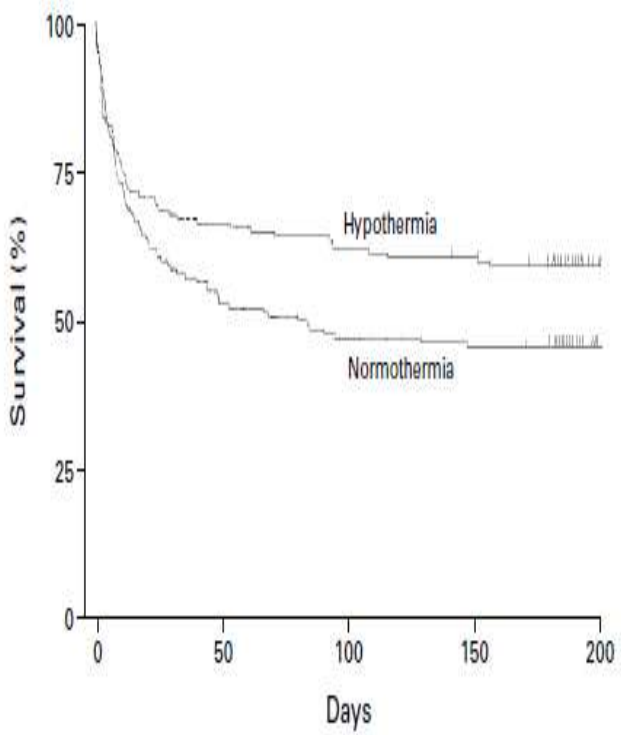


Figure 2. Cumulative Survival in the Normothermia and Hypothermia Groups.

Objectiu secundari

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.

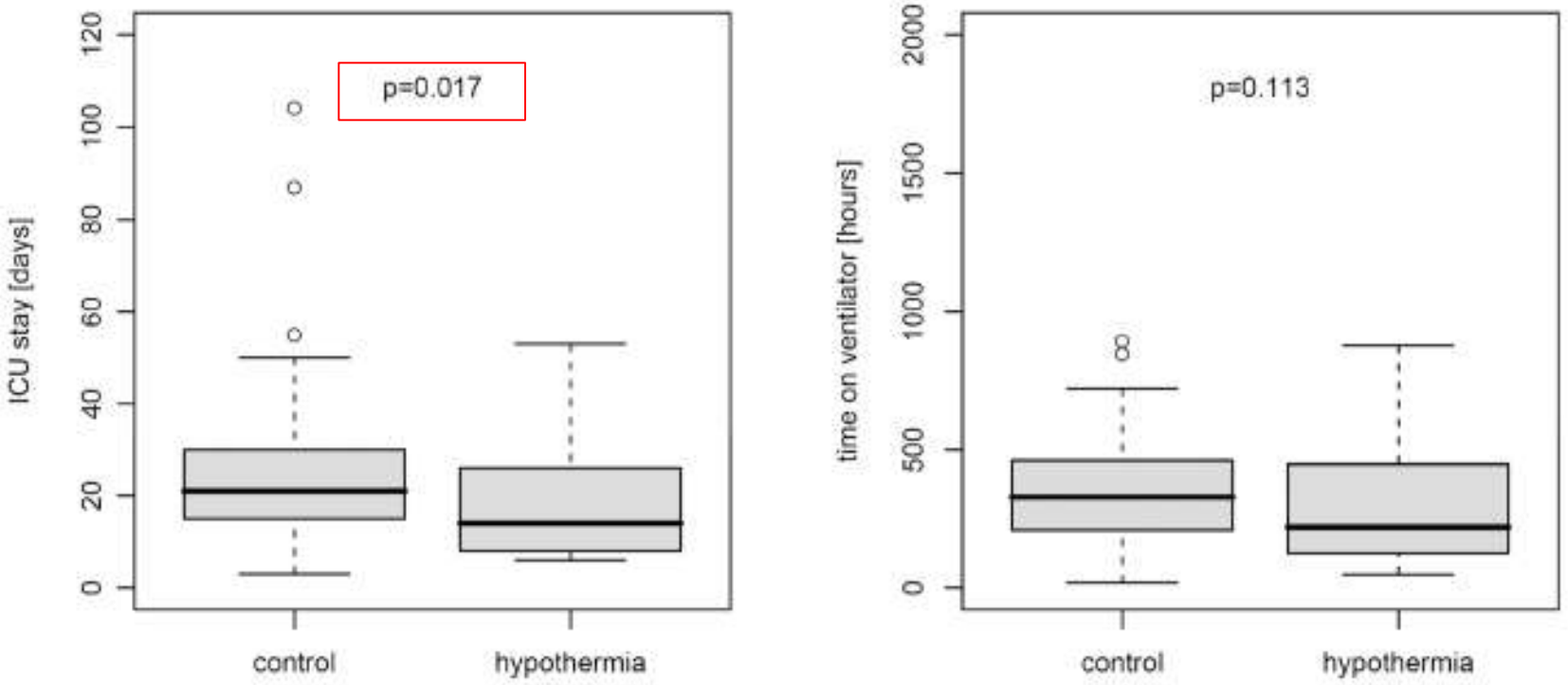
Mild therapeutic hypothermia shortens intensive care unit stay of survivors after out-of-hospital cardiac arrest compared to historical controls

Christian Storm, Ingo Steffen, Joerg C Schefold, Anne Krueger, Michael Oppert, Achim Jörres and Dietrich Hasper

Critical Care 2008

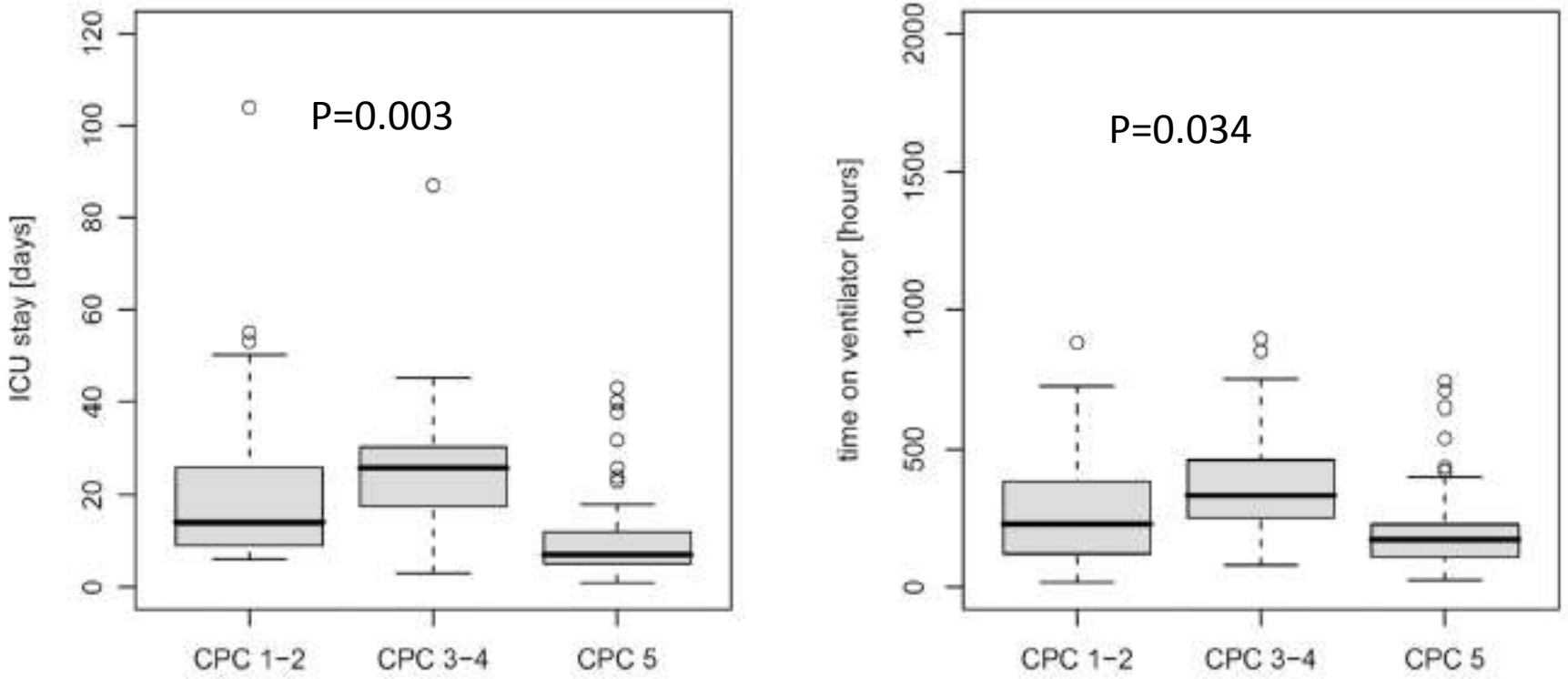
- Estudi prospectiu observacional del grup HT entre 2006-2007.
- Controls històrics de pc amb AC extra-hospitalària entre 2003-2005.
- Objectiu: influència de la HT en la durada de l'estada a UCI i el temps de ventilació mecànica en pacients que sobreviuen a AC.

Resultats



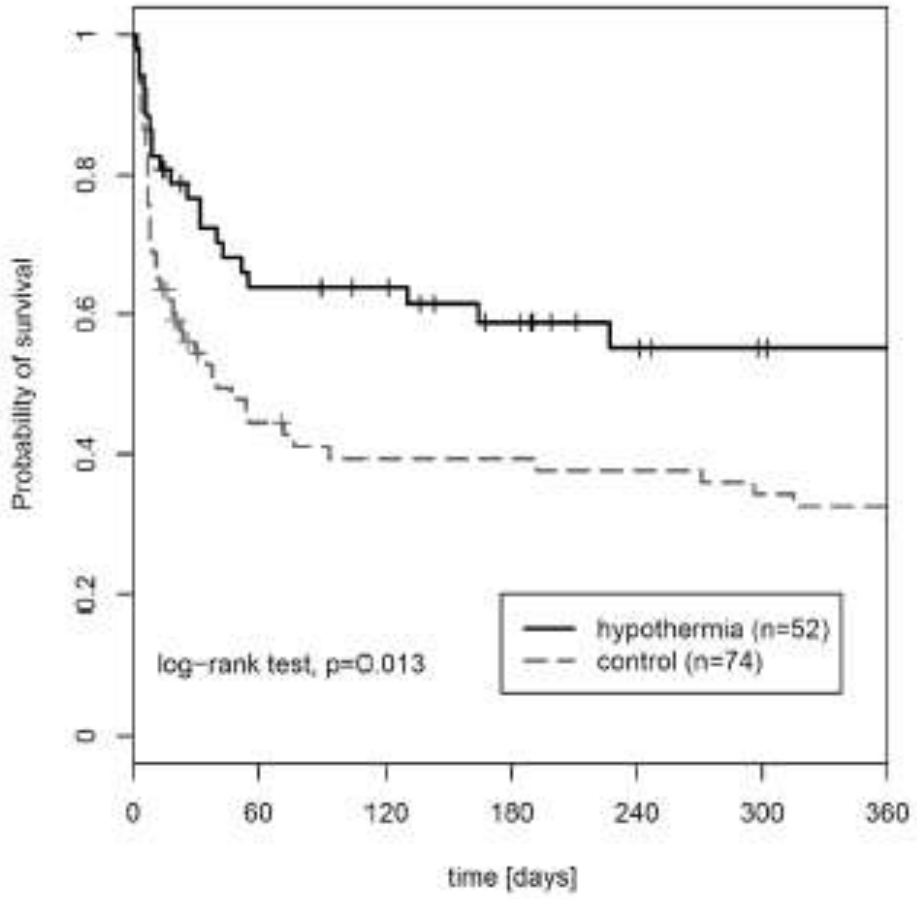
Intensive care unit (ICU) length of stay and time on ventilator in the study groups. Boxplot of ICU length of stay (left) and time on ventilator (right) in survivors of the hypothermia (n = 23) and the control (n = 43) group.

Resultats



Intensive care unit (ICU) length of stay and time on ventilator and neurological outcome. Boxplot of ICU length of stay (left) and time on ventilator (right) of the study population (n = 126) according to the neurological outcome assessed as cerebral performance category (CPC).

Resultats



One-year survival of the study population. Kaplan-Meier 1-year survival analysis of both study groups.

Revisión Cochrane 2012

HIPOTERMIA PARA LA NEUROPROTECCIÓN EN ADULTOS DESPUÉS DE LA REANIMACIÓN CARDIOPULMONAR

Jasmin Arrich, Michael Holzer, Harald Herkner, Marcus Müllner

Revisión Cochrane 2012

· Revisió sistemàtica i metaanàlisis.

·Mesures principals: l'estat neurològic , supervivència hospitalària y efectes adversos.

· Cinc assaigos clínics aleatoritzats (481 pacientes).

· Resultats:

- Grupo d'HT moderada → millor puntuació segons la classificació CPC durant l'ingrés hospitalari.
- Major supervivència a l'alta hospitalària.

No es va detectar diferències significatives en efectes adversos.

I LA QUALITAT DE VIDA???

Cardiac arrest survivors treated with or without mild therapeutic hypothermia: performance status and quality of life assessment

Robert Kowalik[1*], Ewa Szczerba[1], Łukasz Kołtowski[1], Marcin Grabowski[1], Karolina Chojnacka[2], Wojciech Golecki[2], Adam Hołubek[2] and Grzegorz Opolski[1]

Kowalik *et al. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine* 2014, **22**:76

· Estudi observacional, retrospectiu, unicéntric entre 2011-2013.

· Objectiu:

*Determinar l'estat neuropsicològic post-AC extrahospitalària.

*Comparar entre els pacients tractats amb MTH vs control.

· 28 pc adults en HT post-ACR extra-hospitalari vs 37 grup control.

· Escales per valorar l'estat de salut, funcionament i la qualitat de vida:

Disability Rating Scale (DRS); Index de Barthel; RAND 36-Item Sorth Form Health Survey

Funcionament psicosocial i qualitat de vida llarg plaç

Table 5 RAND-36 questionnaire results (the result expressed as rank average is directly proportional to the number of negative assessments of a given domain and inversely proportional to the level of patient functioning in the respective area)

RAND-36 domains	Control group (rank average)	MTH (rank average)	p (U-test)
Role limitations due to emotional problems	18.83	12.17	0.037
Energy/fatigue	16.92	10.08	0.022
Emotional wellbeing	15.07	12.85	0.488
Social functioning	17.59	14.30	0.318
General health	17.71	12.47	0.102

MTH – mild therapeutic hypothermia, $p<0,05$ is considered as significant.

PC en HT presentaven millor qualitat de vida i menys limitacions per problemes emocionals en comparació amb el grup control.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Niklas Nielsen, M.D., Ph.D., Jørn Wetterslev, M.D., Ph.D., Tobias Cronberg, M.D., Ph.D., David Erlinge, M.D., Ph.D., Yvan Gasche, M.D., Christian Hassager, M.D., D.M.Sci., Janneke Horn, M.D., Ph.D., Jan Hovdenes, M.D., Ph.D., Jesper Kjaergaard, M.D., D.M.Sci., Michael Kuiper, M.D., Ph.D., Tommaso Pellis, M.D., Pascal Stammet, M.D., Michael Wanscher, M.D., Ph.D., Matt P. Wise, M.D., D.Phil., Anders Åneman, M.D., Ph.D., Nawaf Al-Subaie, M.D., Søren Boesgaard, M.D., D.M.Sci., John Bro-Jeppesen, M.D., Iole Brunetti, M.D., Jan Frederik Bugge, M.D., Ph.D., Christopher D. Hingston, M.D., Nicole P. Juffermans, M.D., Ph.D., Matty Koopmans, R.N., M.Sc., Lars Køber, M.D., D.M.Sci., Jørund Langørgen, M.D., Gisela Lilja, O.T., Jacob Eifer Møller, M.D., D.M.Sci., Malin Rundgren, M.D., Ph.D., Christian Rylander, M.D., Ph.D., Ondrej Smid, M.D., Christophe Werer, M.D., Per Winkel, M.D., D.M.Sci., and Hans Friberg, M.D., Ph.D., for the TTM Trial Investigators*

DECEMBER 5, 2013

Estudi neutral.

Bona supervivència en ambdós braços.

Sense diferències significatives en quant efectes adversos.

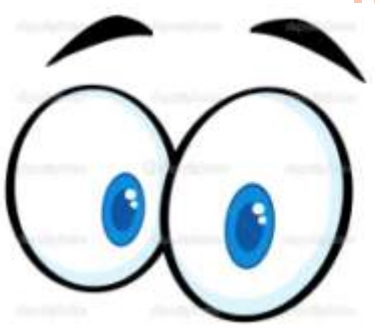
Table 2. Outcomes.

Outcome	33°C Group	36°C Group	Hazard Ratio or Risk Ratio (95% CI)*	P Value
	no./total no. (%)			
Primary outcome: deaths at end of trial	235/473 (50)	225/466 (48)	1.06 (0.89–1.28)	0.51
Secondary outcomes				
Neurologic function at follow-up†				
CPC of 3–5	251/469 (54)	242/464 (52)	1.02 (0.88–1.16)	0.78
Modified Rankin scale score of 4–6	245/469 (52)	239/464 (52)	1.01 (0.89–1.14)	0.87
Deaths at 180 days	226/473 (48)	220/466 (47)	1.01 (0.87–1.15)	0.92

* The hazard ratio is shown for the primary outcome, and risk ratios are shown for the secondary outcomes. CI denotes confidence interval.

† The neurologic follow-up was specified in the protocol to be performed at 180 days ±2 weeks, but the time to follow-up was in some cases several weeks longer for logistic reasons. The Cerebral Performance Category (CPC) scale ranges from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate cerebral disability (function is sufficient for independent activities of daily life), 3 severe cerebral disability, 4 coma or vegetative state, and 5 brain death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.

Diferències amb altres estudis



· Control actiu de la temperatura en ambdós grups: no es compara hipotèrmia vs normotèrmia.

· Cures post-ressuscitació → poden emmascarar l'efecte beneficiós de la HT.

. No hi ha uniformitat en quant el mètode de refredament: 24% mètodes endovasculars / 76% mètodes de superfície.

Variabilitat en la temperatura

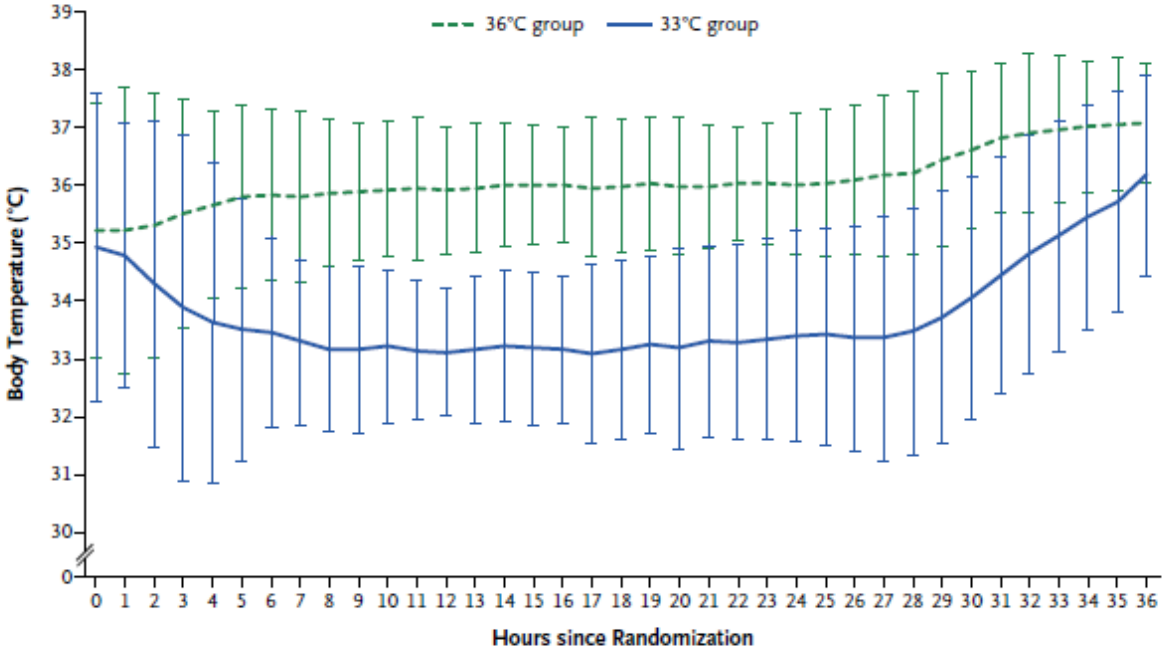


Figure 1. Body Temperature during the Intervention Period.

Shown are body-temperature curves in the 33°C and 36°C groups for the 860 patients in whom a bladder temperature was recorded. In the remaining 79 patients, the temperature was recorded with an intravascular or esophageal probe, with a similar temperature profile (data not shown). Rewarming was commenced at 28 hours after randomization. The temperature curves display the means, and the I bars indicate ±2 SD (95% of the observations are within the error bars).

TABLE I.—*Major differences among the three randomized trials on the use of therapeutic hypothermia after cardiac arrest.*

	HACA (2002) [7] N.=275	Bernard (2002) [6] N.=77	TTM (2013) [16] N.=939
Median age (years)	59	66	64
Gender, N. (%)	210/275 (76%)	52/77 (68%)	761/939 (81)
Initial Rhythm	VF/VT	VF	VF/VT = 752/939 (80%)
Witnessed CA, N. (%)	99%	95%	90%
Study period	1996-2001	1996-1999	Nov 2010 – Jan 2013
Bystander CPR, N. (%)	127/275 (46%)	45/77 (58%)	683/939 (73%)
Epinephrine, mg	3 [1-6]	2.2 ± 2.1	NA
Median time to ROSC, min	22	26	25
Thrombolysis, N. (%)	51/275 (19%)	NA	20/930 (2%) *
Hypothermia, hrs	24	12	24
Duration of rewarming, hrs	8	6	8
Post-resuscitation care	No	Yes	No
Prognostication	No	No	Yes
Survival			
All cohort	52%	41%	52%
VF/VT	52%	41%	60%
Hypothermia	59%	49%	50% #
Intact Neurological outcome			
All cohort	47%	31%	48%
VF/VT	47%	31%	NA
Hypothermia	55%	49%	NA

VF: ventricular fibrillation; VT: ventricular tachycardia; CA: cardiac arrest; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; NA: not available.
*44% of patients had percutaneous coronary intervention (PCI)
#33 °C Group

Minerva Anestiol 2014

Time from cardiac arrest to event — min‡		
Start of basic life support	**33°C Group**	**36°C Group**
Median	1	1
Interquartile range	0–2	0–2

EL PRONÒSTIC

Table S8. **Neurological prognostication***			
	33°C	36°C	Total
Total no.	473	466	939
Prognostication performed no. (%)	172 (36)	148 (32)	320 (34)
Recommendation no. (%)			
Continue care	65 (38)	52 (35)	117 (37)
Do not escalate	32 (19)	24 (16)	56 (17)
Withdraw care	73 (42)	71 (48)	144 (45)
Recommendation not recorded	2	1	3
Hours from CA to prognostication median (IQR)	117 (93-137)	119 (94-141)	118 (93-140)
Prognostication not performed no. (%)	16 (3)	15 (3)	31 (3)
Reasons no.			
Sedation Days with sedation affecting neurological evaluation median [IQR]	2 [2-3]	2 [1-3]	2 [1-3]
Died before prognostication no. (%)	76 (16)	62 (13)	138 (15)
Presumed cause of death no. (%)			
Cardiac/hemodynamic cause	36 (47)	27 (43)	63 (46)
Multi organ failure	19 (25)	12 (19)	31 (22)
Cerebral cause	21 (28)	23 (37)	44 (32)
WLST of patients who died before reported prognostication no. (%)	48 (63 %)	42 (68 %)	90 (65 %)
Regained consciousness before prognostication no. (%)**	209 (44 %)	241 (52 %)	450 (48 %)

P=0.03

Table 3. Neurologic Scores.*

Variable	33°C Group	36°C Group
CPC at follow-up†		
Total no. of patients	469	464
Category — no. (%)		
1	195 (42)	183 (39)
2	23 (5)	39 (8)
3	17 (4)	20 (4)
4	6 (1)	2 (0.5)
5	228 (49)	220 (47)

- Peró……

- I la qualitat de vida més enllà del 6 mesos??
- I la funció cognitiva???

MOLTES GRÀCIES!!!!