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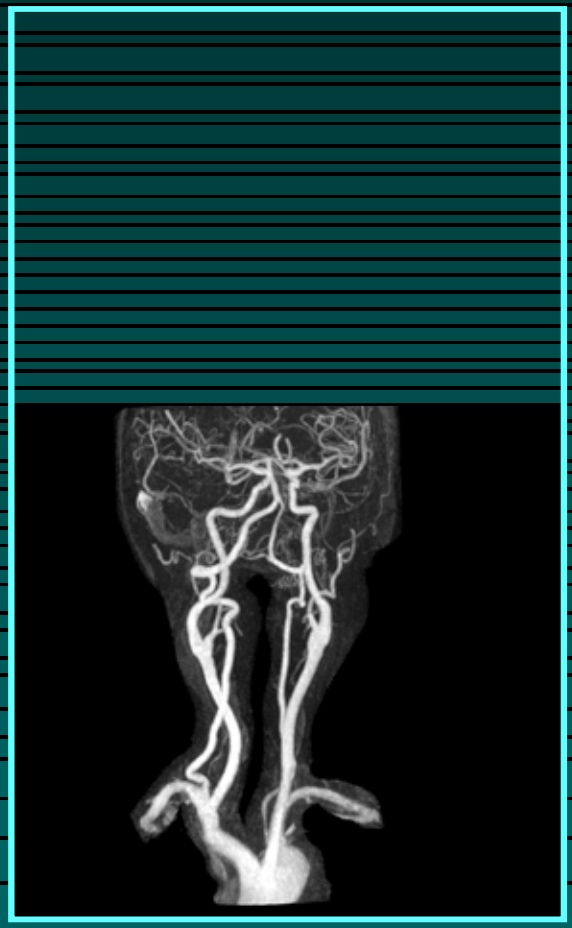
Postresuscitation Coma and Therapeutic Hypothermia

Eelco F. M. Wijdicks, MD

Mayo College of Medicine

Pathology

- Cortical laminar necrosis
- Watershed zones
- Basal ganglia
- Pyramidal layers Hippocampus
- Purkinje cells



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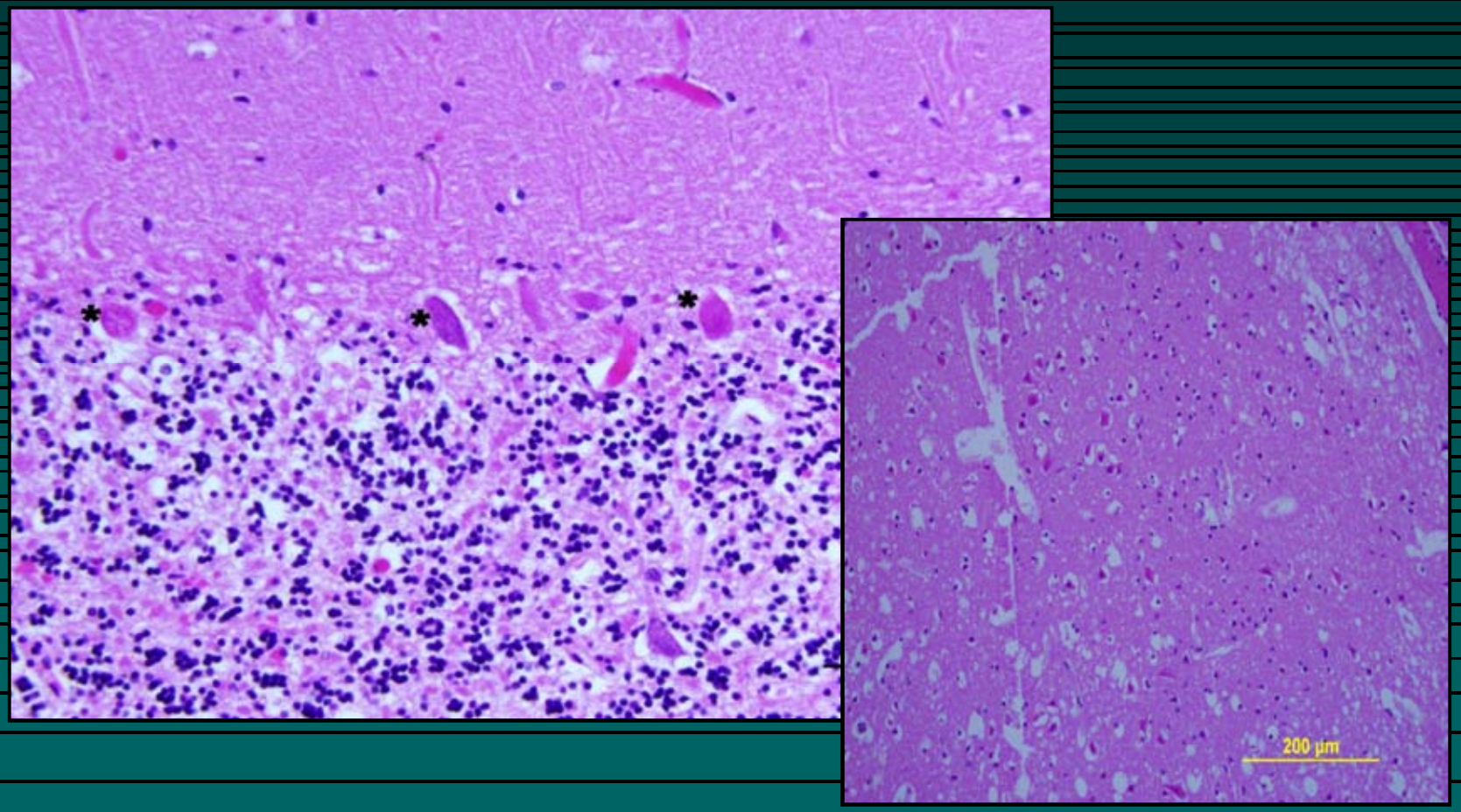
Purkinje and Cortical Cell Loss



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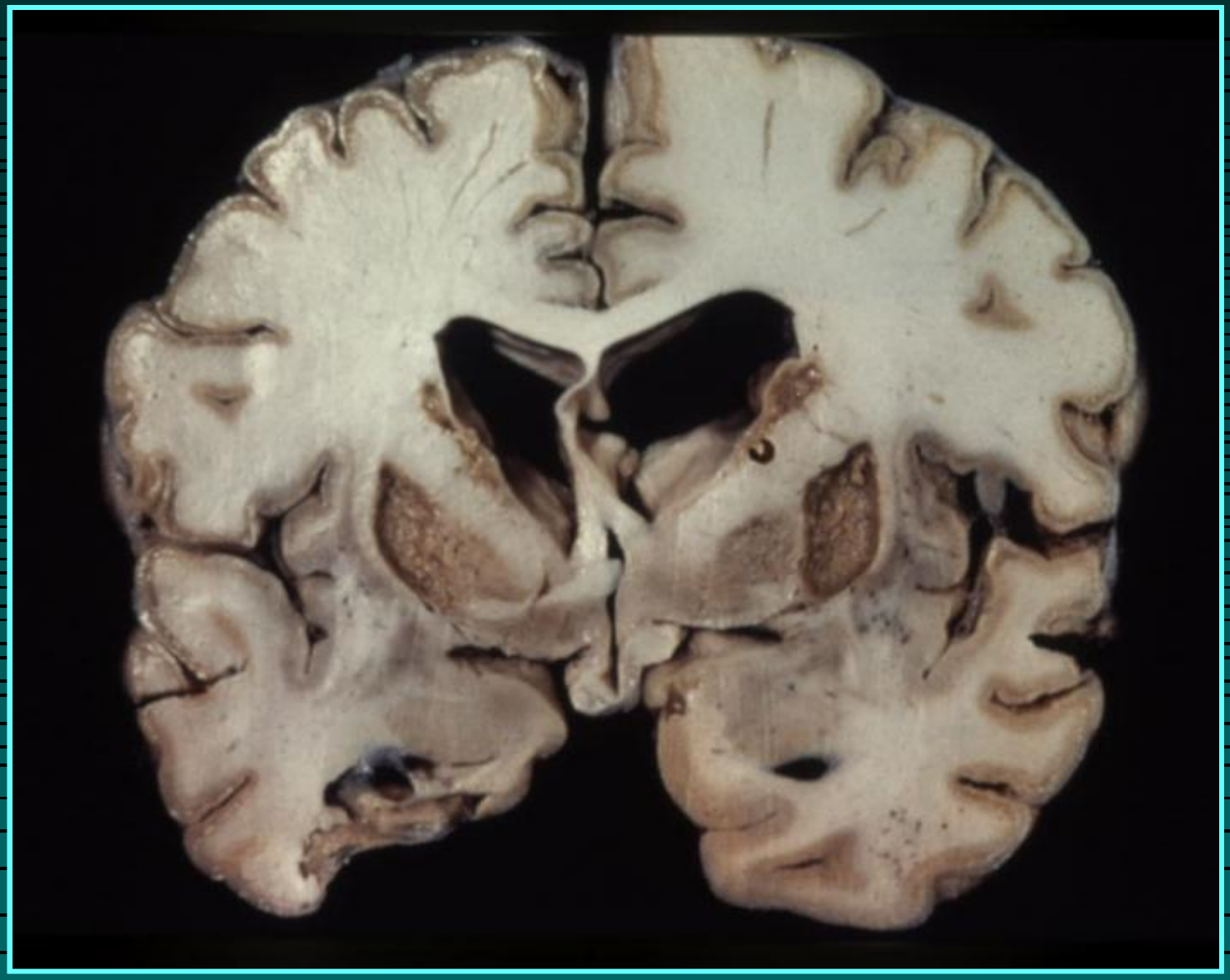

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Prognostication

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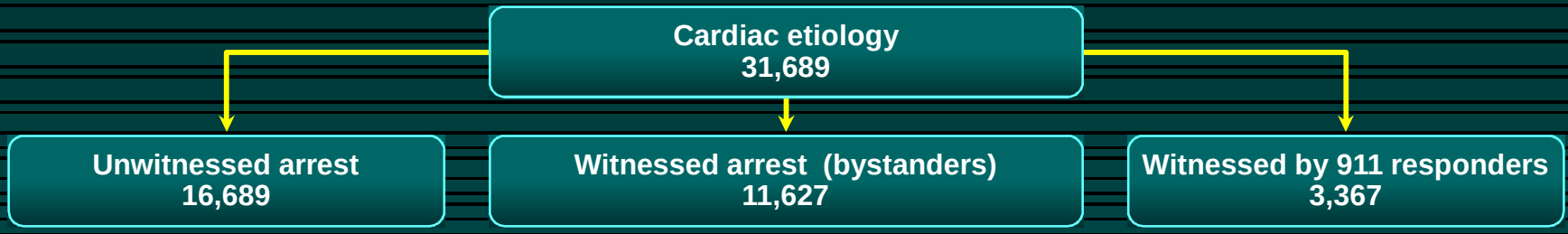
Utstein Survival Report



McNally et al: CDC Surveillance Summaries 60(SS08), July 29, 2011

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Utstein Survival Report

McNally et al: CDC Surveillance Summaries 60(SS08), July 29, 2011

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Clinical Features

- Best motor response
- Eye findings
- Myoclonus

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Pain Stimuli

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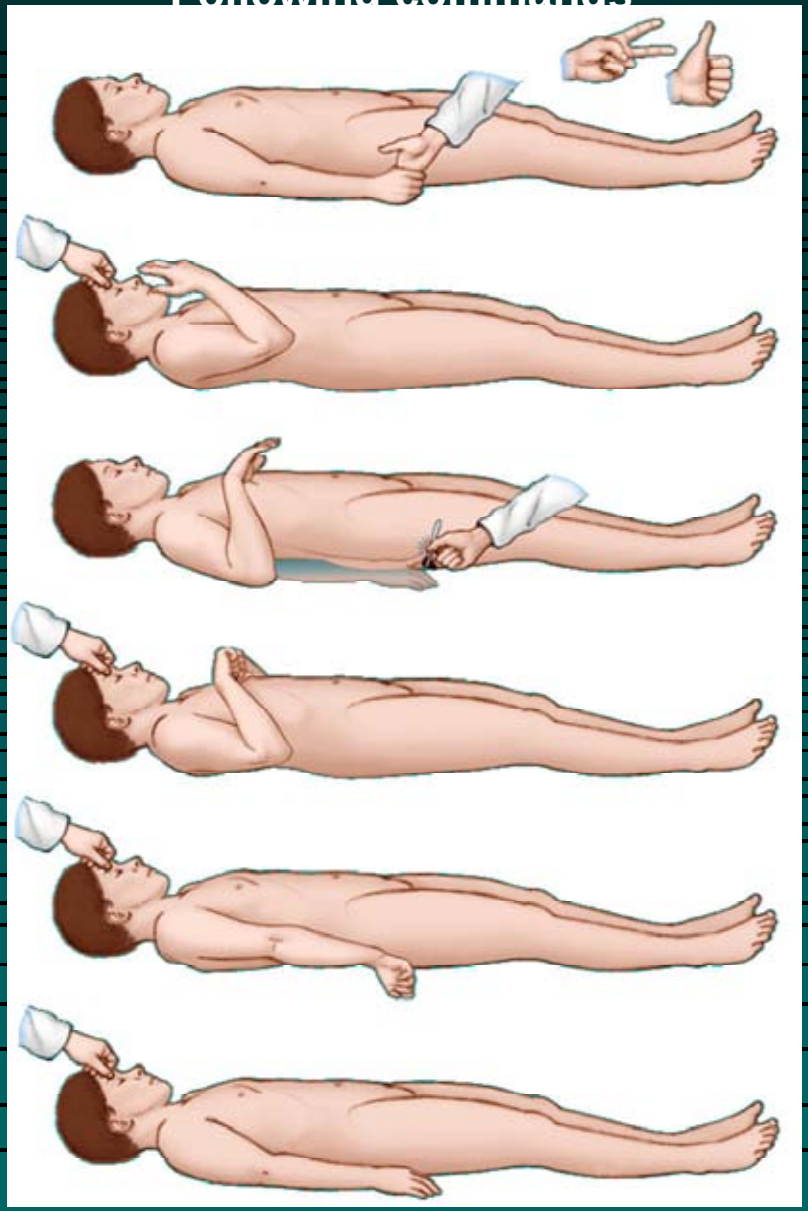
Following commands



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Normal pupil size

Oculomotor palsy from acute intracranial mass

Mydriasis (anxiety, delirium, pain, seizures, atropine, dopamine)

Midposition pupils: Brain death; diencephalic herniation

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Eye Findings

Feature	Pathology
• Ocular dipping	• Diffuse cortex, thalamus
• Ocular bobbing	• Pons, cerebellum
• Upward gaze	• Nonlocalizing
• Periodic Lateral gaze	• Nonlocalizing, diffuse cortex
• Ping-pong	• Nonlocalizing, diffuse cortex

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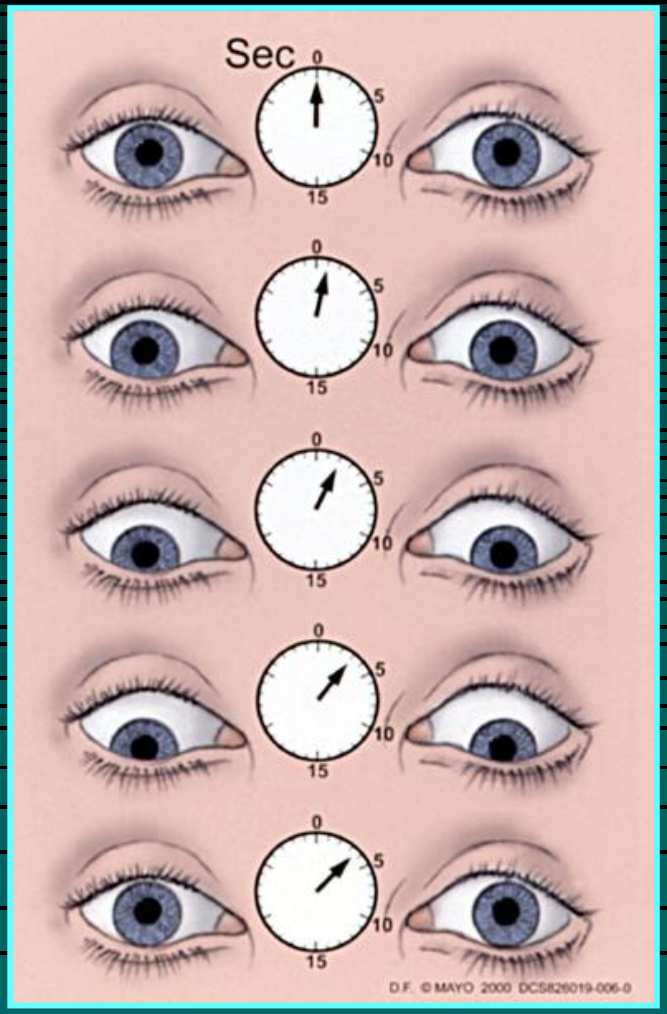
Dipping



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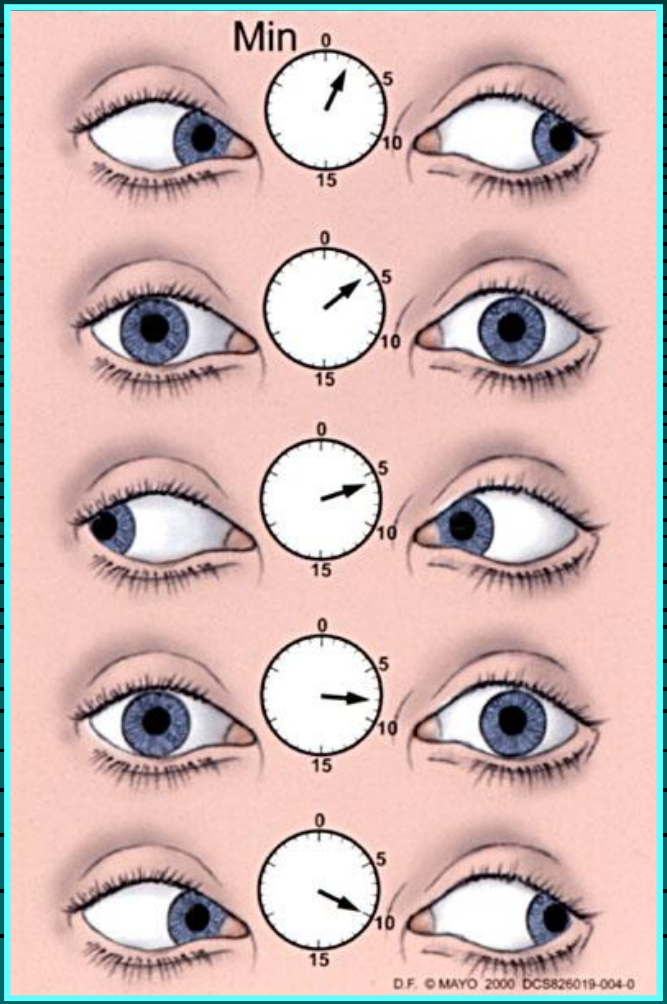
Periodic Alternating



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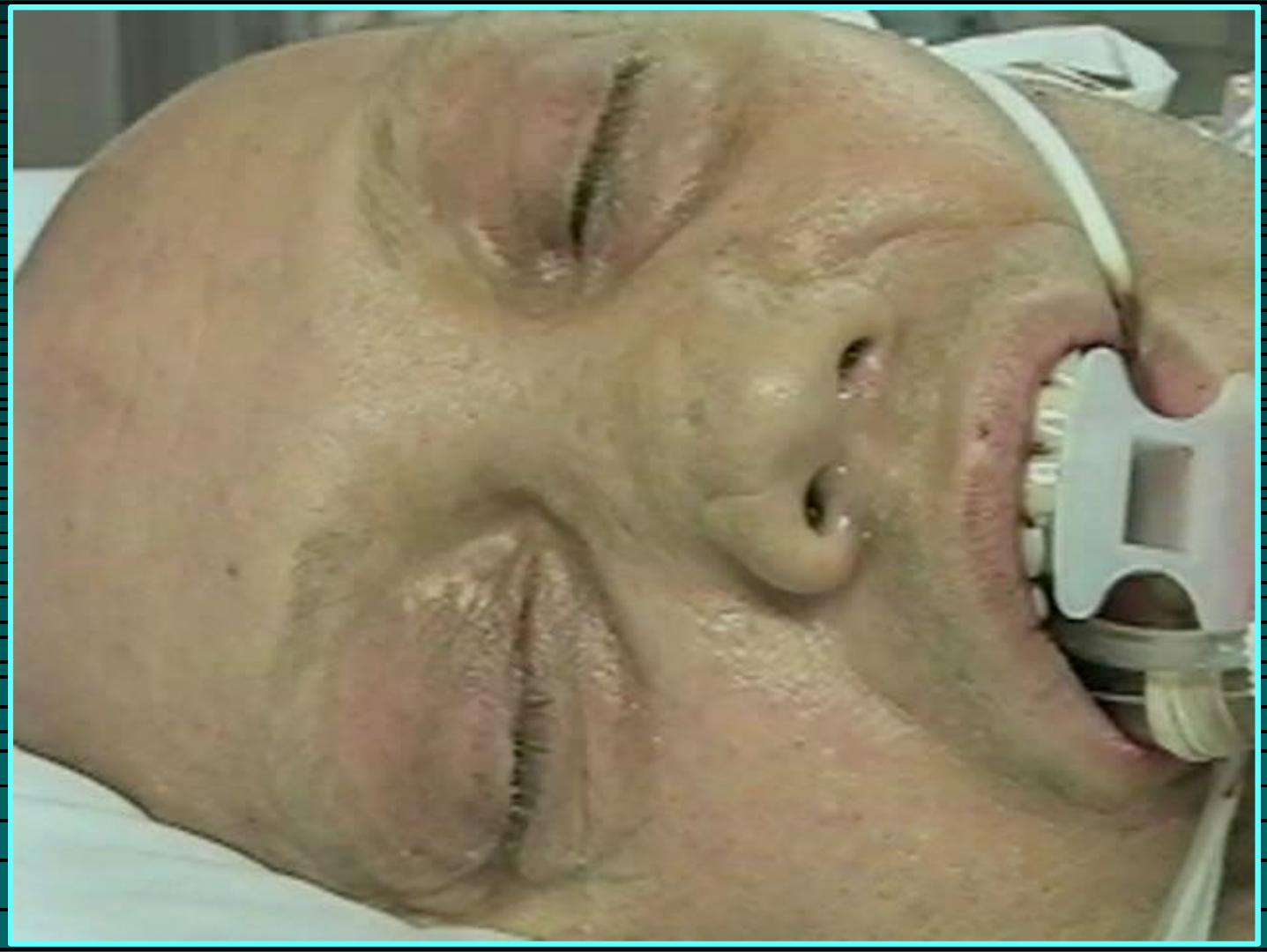

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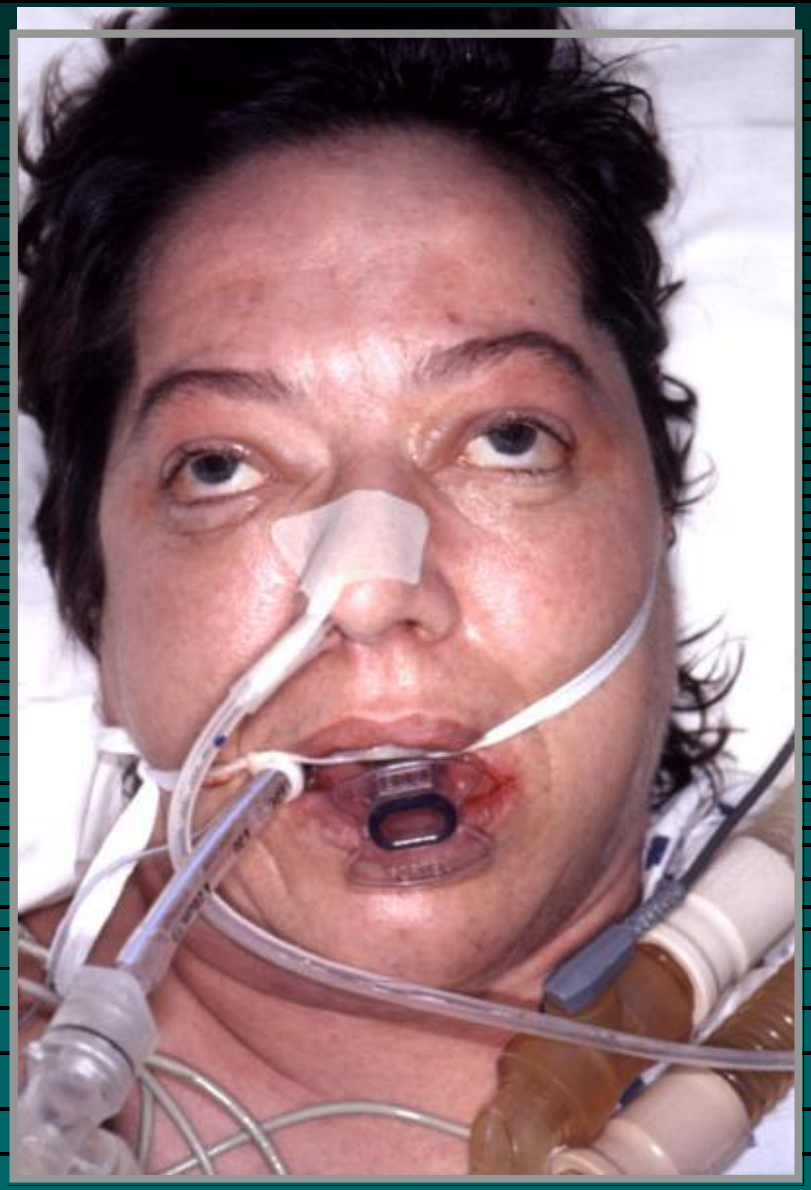

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Sustained Upward Gaze in Postresuscitation Coma

- Not epileptic phenomenon
- 2 weeks-2 months
- Often with myoclonus
- Outcome invariably poor
  - Vegetative state – death

Keane et al, 1981

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Post arrest myoclonic status

- Cardiac arrest
- Gone within a few days
- Severe brain damage on physical exam and ancillary tests
- Electroencephalogram often with burst suppression
- Hopeless condition

Posthypoxic action myoclonus

- Usually after respiratory arrest
- Persists
- No evidence of severe brain damage on physical exam and ancillary tests
- Electroencephalogram often diffuse slowing
- Good cognitive recovery but ataxia

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Myoclonus Status Epilepticus

- Agonal phenomenon
- Rapid, brief, jerks
- Face, limbs, diaphragm
- Sound and touch sensitive
- Disappears in 1-2 days

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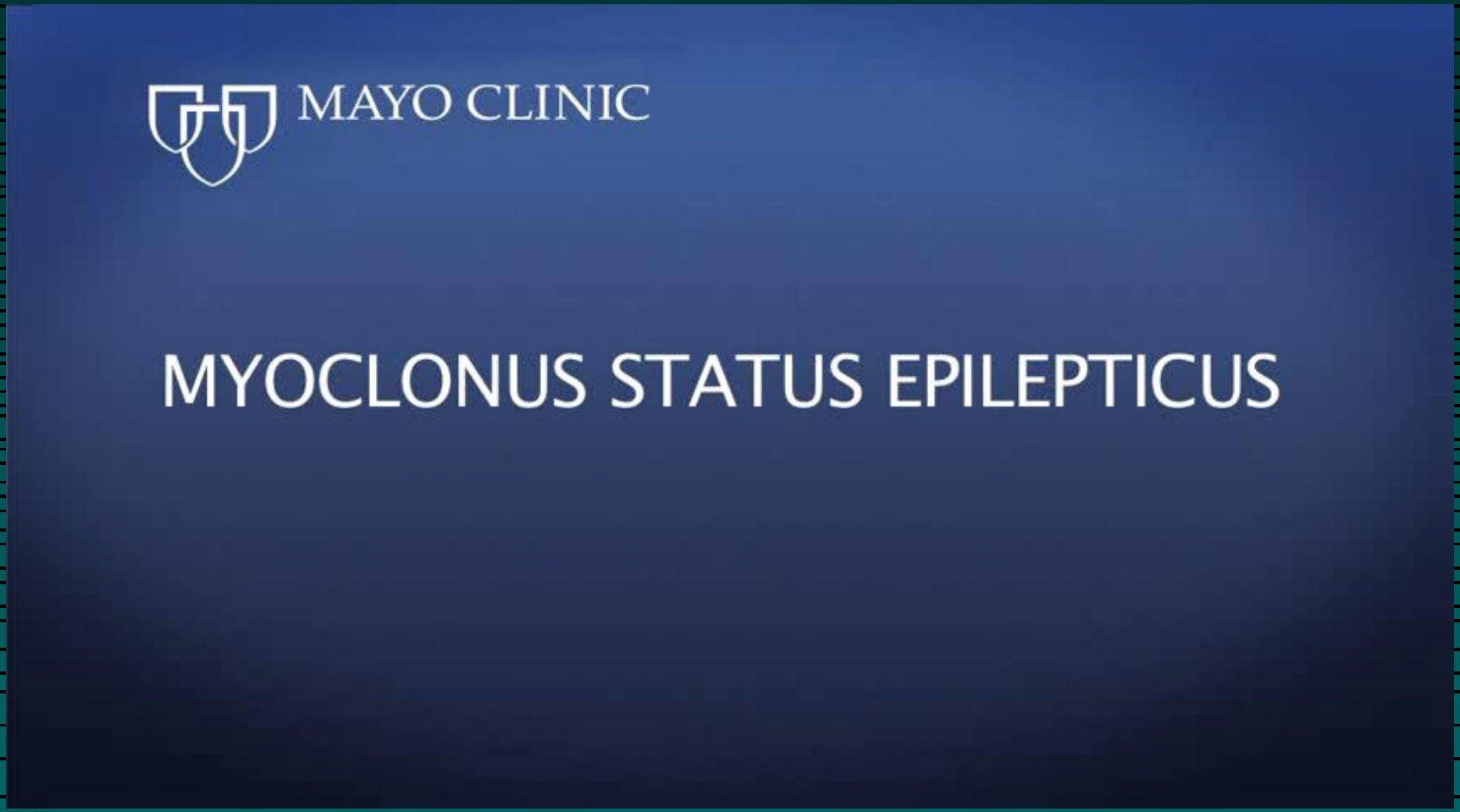

107 Comatose Survivors of Cardiac Arrest

	Myoclonus status (n=40)		No myoclonus status (n=67)	
Feature	**No**	**%**	**No.**	**%**
EEG findings				
Burst suppression	33	83	5	7
Polyspike waves	3	8	2	3
PLEDs	0	–	4	6
Alpha coma	3	8	2	3
Diffuse slowing	1	3	44	66
CT scan				
Cerebral infarcts	6	41	1	10
Cerebral edema	6	41	3	10
Normal	17	–	38	–
Outcome				
Awakened	0	–	20	30
Poor outcome or death	40	100	52	78
Good outcome	0	–	15	22

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Outcome of Myoclonic Status Epilepticus in Survivors of Cardiac Arrest

Reference	Pt (no.)	Surviving to hospital dismissal (no.)
Celesia et al	13	1
Krumholtz et al	19	0
Jumao-as and Brenner	15	0
Wijdicks et al	40	0
Young et al	18	0
Thomke et al	50	0
Total	155	2 (1%)

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Laboratory Tests

- EEG
- SSEP
- CT/MR
- Biomarkers

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Classification for Electroencephalographic Findings After Resuscitation from Cardiac Arrest

EEG Grade	Finding
I	Normal alpha with theta-delta activity
II	Dominant theta-delta activity with detectable normal alpha
III	Dominant theta-delta activity without detectable normal alpha
IV	(A) Low-voltage delta, possible with short isoelectric intervals (burst suppression)
	(B) Dominant, monomorphic nonreactive alpha activity (alpha coma)
	(C) Periodic generalized phenomena (eg, spikes, sharp waves, slow waves with very low background activity)
V	Suppressed to isoelectric electroencephalogram

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Literature Review of Electroencephalographic Findings After Resuscitation from Cardiac Arrest

EEG grade	Full recovery		Survival with neurological sequela		Death	
	No. (%)	95% CI	No. (%)	95% CI	No. (%)	95% CI
I	48 (79)	66-81	6 (10)	4-20	7 (11)	5-22
II	45 (51)	40-62	11 (13)	6-21	32 (36)	26-47
III	11 (27)	14-43	3 (7)	2-20	27 (66)	49-81
IV	0 (0)	0-3	3 (2)	0.5-6	135 (98)	94-100
V	0 (0)	0-5	0 (0)	0-5	70 (100)	95-100

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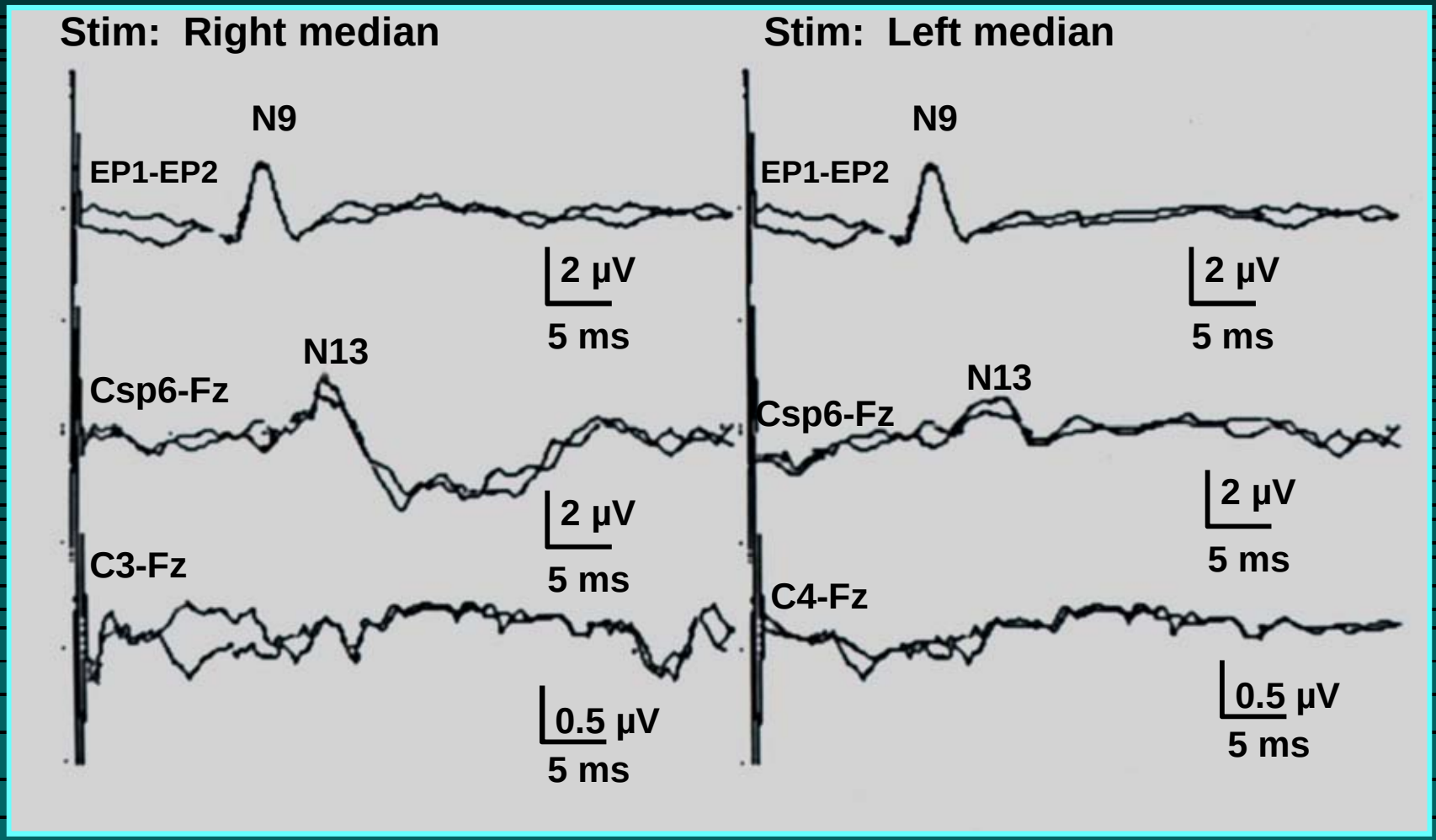
?SEP in Postanoxic Coma”



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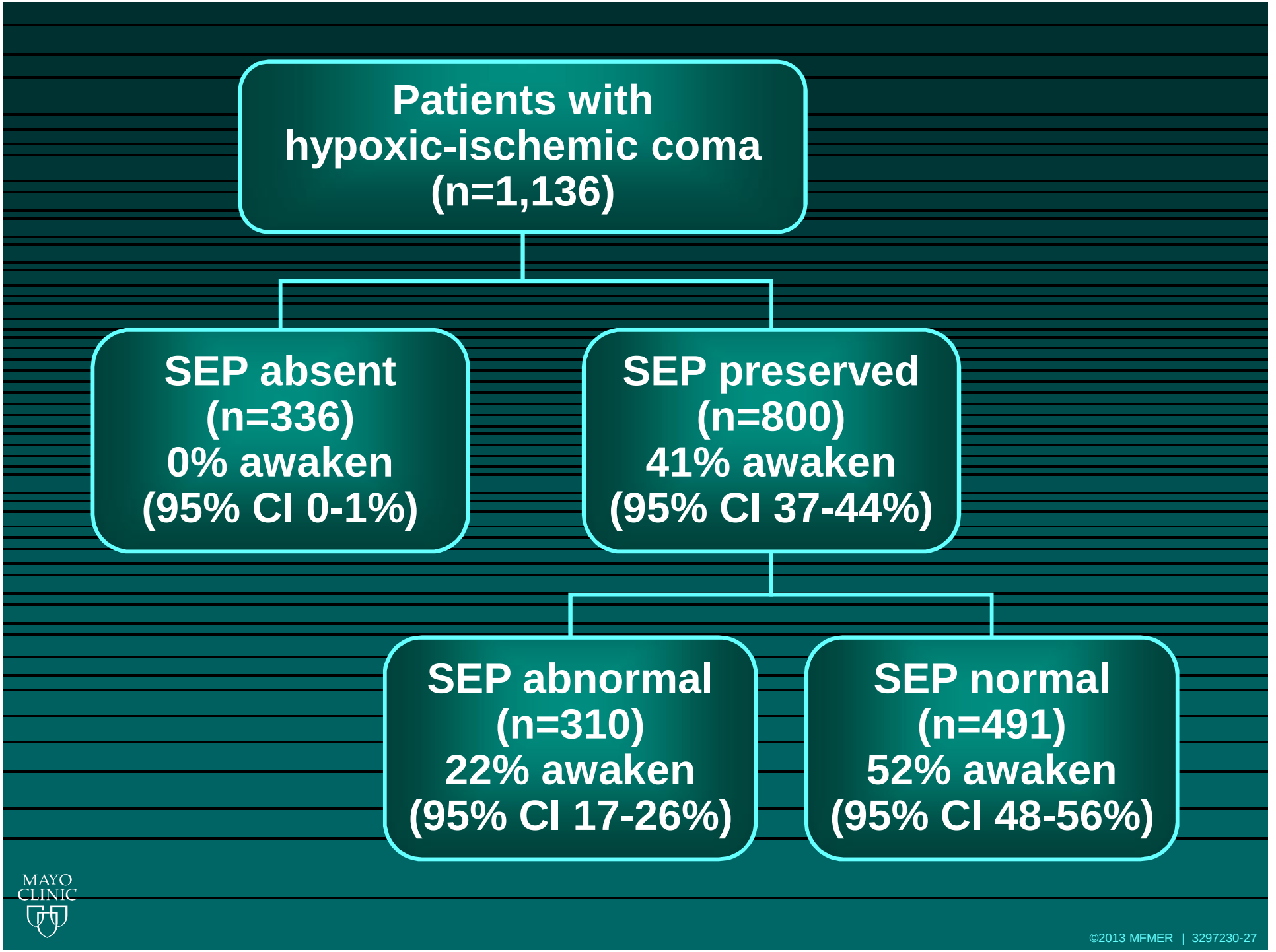

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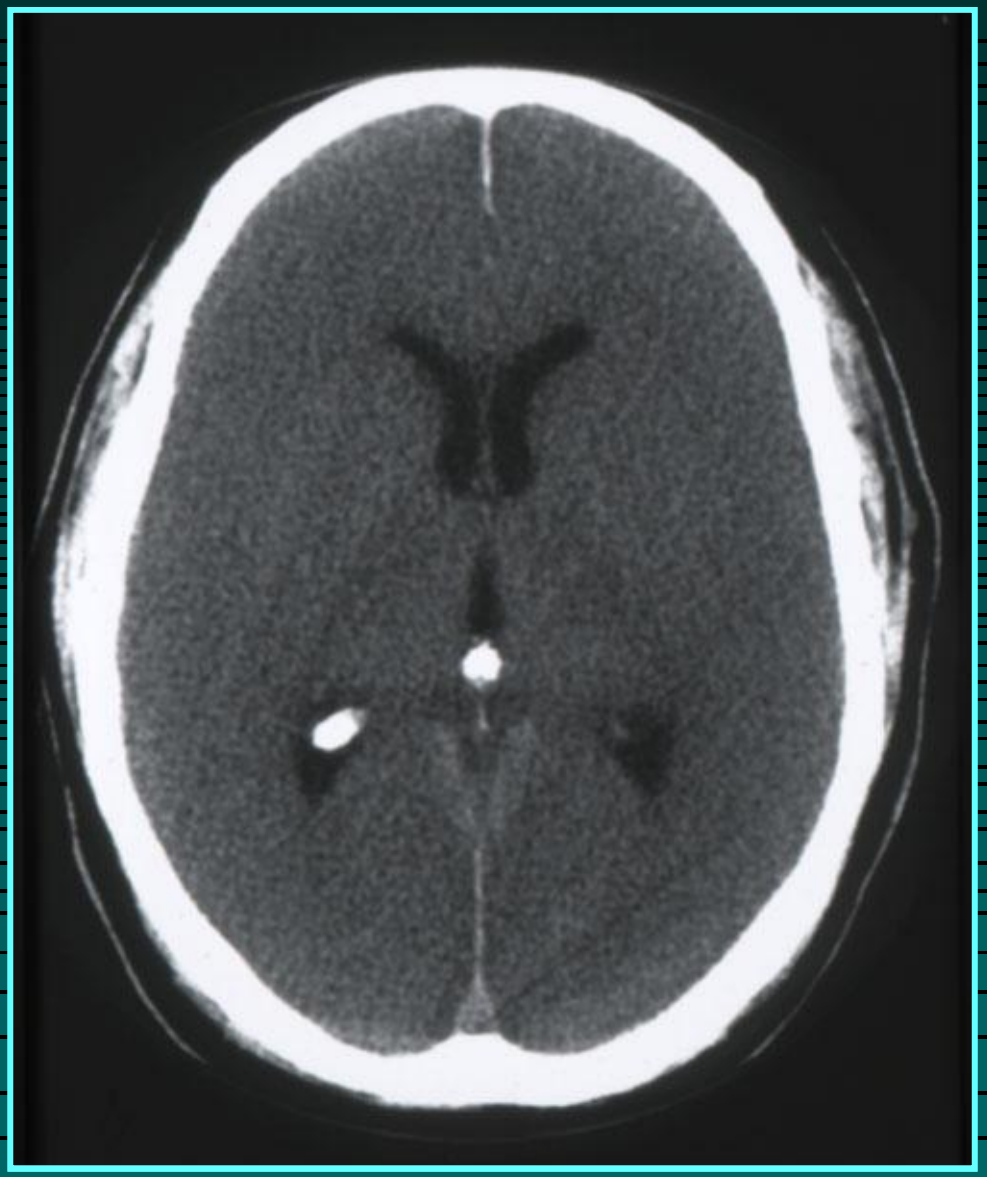

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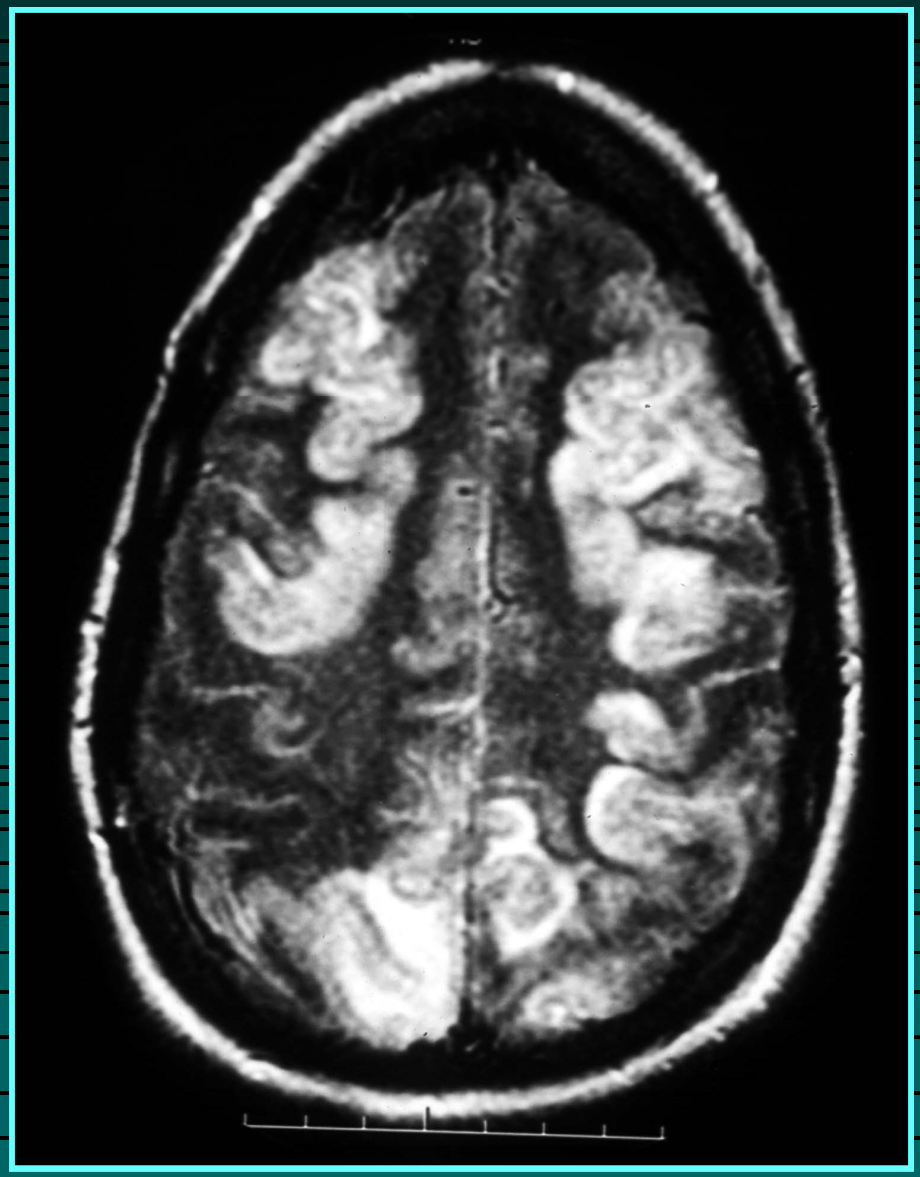

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MRI Studies After CPR

- Small series (<100 patients)
- Widespread areas of reduced diffusion in the cortex >48 hours predicts poor outcome
- Not validated in patients with hypothermia
- Repeatedly normal MRI may be associated with poor outcome

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Available online http://ccforum.com/content/10/5/R133

Research

Open Access

Serum neuron-specific enolase as early predictor of outcome after in-hospital cardiac arrest: a cohort study

Tatiana H Rech[1], Silvia Regina Rios Vieira[1], Fabiano Nagel[2], Janete Salles Brauner[1] and Rosana Scalco[3]

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Critical Care 2006, **10**:R133 (doi:10.1186/cc5046)
This article is online at: http://ccforum.com/content/10/5/R133

Abstract

Introduction Outcome after cardiac arrest is mostly determined by the degree of hypoxic brain damage. Patients recovering from cardiopulmonary resuscitation are at great risk of subsequent death or severe neurological damage, including persistent vegetative state. The early definition of prognosis for these patients has ethical and economic implications. The main purpose of this study was to investigate the prognostic value of serum neuron-specific enolase (NSE) in predicting outcomes in patients early after in-hospital cardiac arrest.

Methods Forty-five patients resuscitated from in-hospital cardiac arrest were prospectively studied from June 2003 to January 2005. Blood samples were collected, at any time between 12 and 36 hours after the arrest, for NSE measurement. Outcome was evaluated 6 months later with the Glasgow outcome scale (GOS). Patients were divided into two groups: group 1 (unfavorable outcome) included GOS 1 and 2 patients; group 2 (favorable outcome) included GOS 3, 4 and 5 patients. The Mann–Whitney *U* test, Student's *t* test and Fisher's exact test were used to compare the groups.

Results The Glasgow coma scale scores were 6.1 ± 3 in group 1 and 12.1 ± 3 in group 2 (means ± SD; $p < 0.001$). The mean time to NSE sampling was 20.2 ± 8.3 hours in group 1 and 28.4 ± 8.7 hours in group 2 ($p = 0.013$). Two patients were excluded from the analysis because of sample hemolysis. At 6 months, favorable outcome was observed in nine patients (19.6%). Thirty patients (69.8%) died and four (9.3%) remained in a persistent vegetative state. The 34 patients (81.4%) in group 1 had significantly higher NSE levels (median 44.24 ng/ml, range 8.1 to 370) than those in group 2 (25.26 ng/ml, range 9.28 to 55.41; $p = 0.034$).

Conclusion Early determination of serum NSE levels is a valuable ancillary method for assessing outcome after in-hospital cardiac arrest.

Introduction

Since the introduction of closed-chest cardiac massage in 1960 [1] there have been several advances in cardiopulmonary resuscitation [2]. In spite of that, morbidity and mortality associated with cardiac arrest remain extremely high [3,4], with prognosis ranging from mild to moderate disability to persistent vegetative state. It is estimated that 80% of sudden death survivors remain in a coma for various lengths of time, and a full neurological recovery is still rare [5]. The possibility of irreversible anoxic brain damage must be taken into account soon after the arrest.

In this scenario, an accurate prognostic evaluation of cardiac arrest patients may have major ethical and economic consequences. Currently, prognosis is based on several clinical, neuroimaging and electrophysiological methods [6-9]. However, applying these methods is often difficult as a result of sedation and the hemodynamic instability commonly seen in

CI = confidence interval; GCS = Glasgow coma scale; GOS = Glasgow outcome scale; NSE = neuron-specific enolase; SSEP = somatosensory evoked potential.

Studies of Serum Neuron-Specific Enolase to Predict Unfavorable Outcome After Cardiac Arrest

Ref	In-hospital CPR	NSE sampling time (hr)	Favorable outcome (no.)	Unfavorable outcome (no.)	Cut-off value (ng/mL)	Sensi-tivity (%)	Specif-icity (%)
[26]	No	24	45	20	>17	40	98
[23]	Not specified	24	27	35	>20	51	89
[12]	No	72	18	25	>33	65	100
[24]	No	72	28	24	>16.4	70	100
[25]	Yes/No[a]	48	34	76	>25	59	100
[13]	Yes/No[b]	72	28	69	>65	50	96
[27]	Yes/No[c]	24	51[d]	356[d]	>33	44	100

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Prediction of outcome in comatose survivors after cardiopulmonary resuscitation

E.F.M. Wijdicks, MD; A. Hijdra, MD; G.B. Young, MD; C.L. Bassetti, MD; and S. Wiebe, MD

Abstract—*Objective:* To systematically review outcomes in comatose survivors after cardiac arrest and cardiopulmonary resuscitation (CPR). *Methods:* The authors analyzed studies (1966 to 2006) that explored predictors of death or unconsciousness after 1 month or unconsciousness or severe disability after 6 months. *Results:* Thee authors identified four class I studies, three class II studies, and five class III studies on clinical findings and circumstances. The indicators of poor outcome after CPR are myoclonus status epilepticus (level B), absent pupillary light response or corneal reflexes, and extensor or no motor response to pain after 3 days of observation (level A). Prognosis cannot be based on circumstances of CPR (level B) or elevated body temperature (level C). The authors identified one class I, one class II, and nine class III studies on electrophysiology. Bilateral absent cortical responses on somatosensory evoked potential studies recorded 3 days after CPR predicted poor outcome (level B). Burst suppression or generalized epileptiform discharges on EEG predicted poor outcomes but with insufficient prognostic accuracy (level C). The authors identified one class I, 11 class III, and three class IV studies on biochemical markers. Serum neuron-specific enolase higher than 33 μg/L predicted poor outcome (level B). Ten class IV studies on brain monitoring and neuroimaging did not provide data to support or refute usefulness in prognostication (level U). *Conclusion:* Pupillary light response, corneal reflexes, motor responses to pain, myoclonus status epilepticus, serum neuron-specific enolase, and somatosensory evoked potential studies can reliably assist in accurately predicting poor outcome in comatose patients after cardiopulmonary resuscitation for cardiac arrest.

NEUROLOGY 2006;67:1–1

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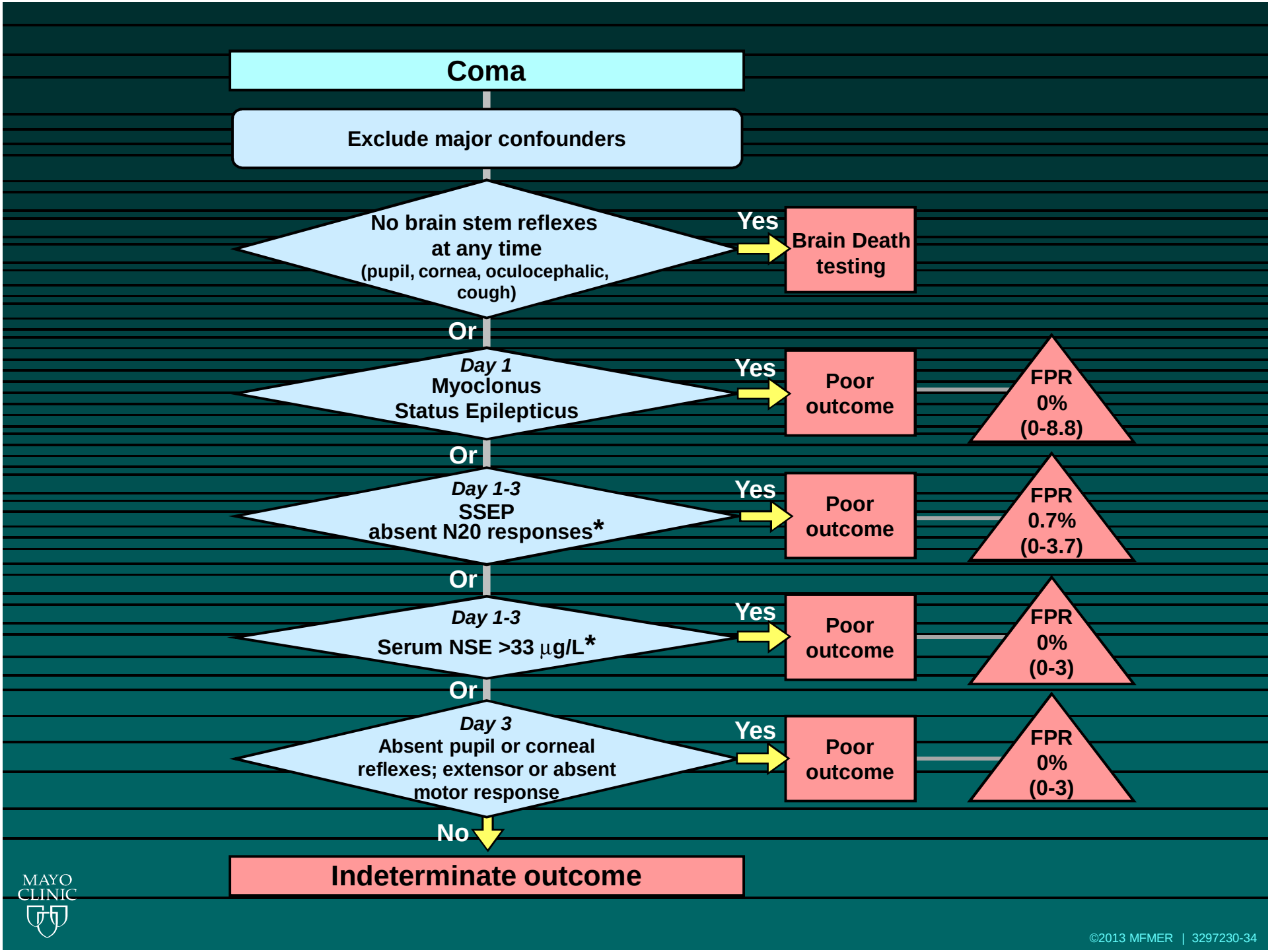

Comatose CPR

Day 1	%
Myoclonus status epilepticus	20
Abnormal SSEP	30
Abnormal NSE	20
Poor outcome	50

Day 3	%
Abnormal SSEP	10
Abnormal brain stem	10
Poor outcome	20

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Improving Outcome

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The New England
Journal of Medicine

Volume 314 FEBRUARY 13, 1986 Number

RANDOMIZED CLINICAL STUDY OF THIOPENTAL LOADING IN COMATOSE SURVIVORS OF CARDIAC ARREST

BRAIN RESUSCITATION CLINICAL TRIAL I STUDY GROUP*

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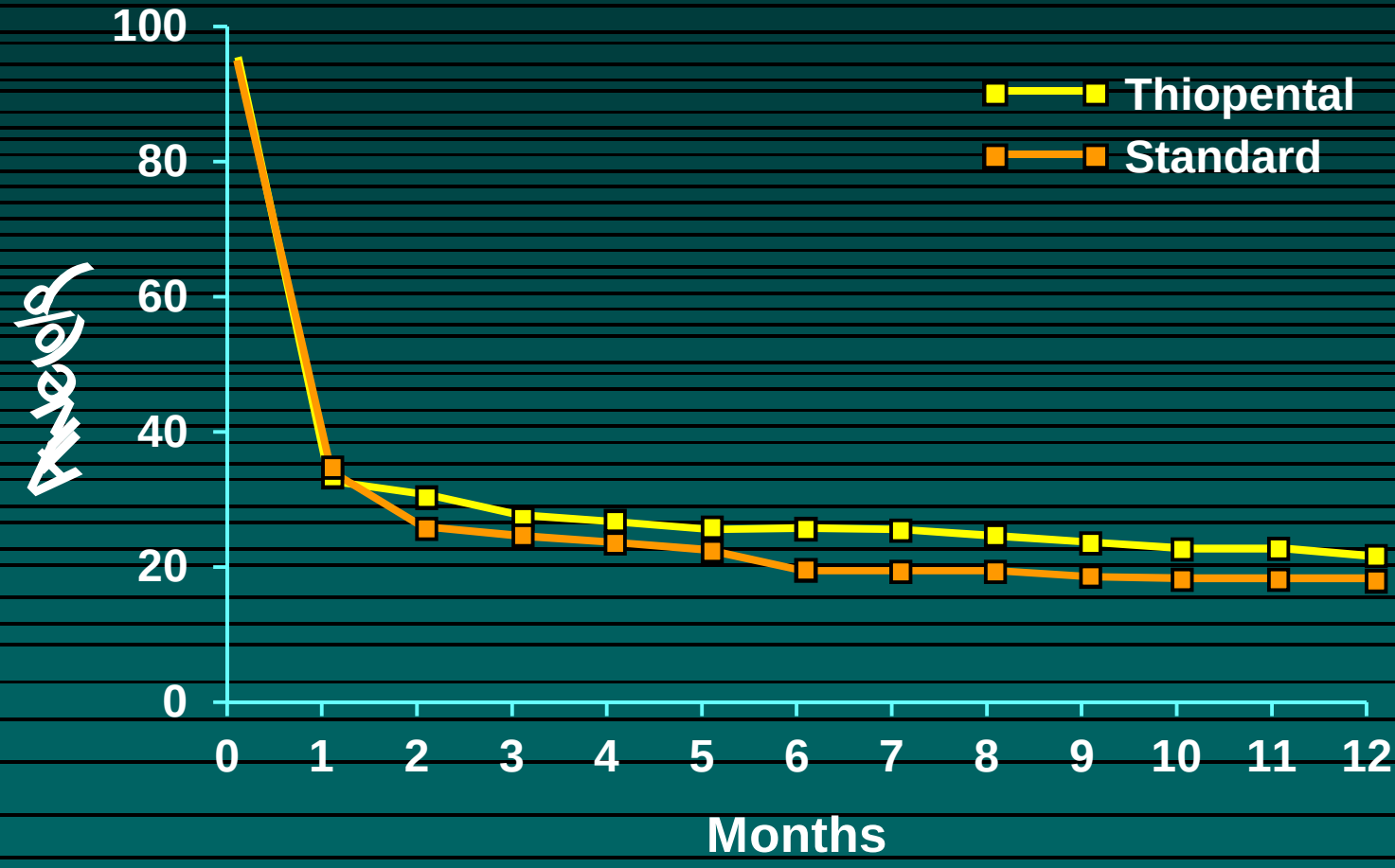
1-Year Cumulative Survival in Patients with Cardiac Arrest Who Remained Comatose



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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*

INDUCED HYPOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST

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.

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Hypothermia Definitions

- Mild 33-36°C
- Moderate 28-32°C
- Deep less than 28°C

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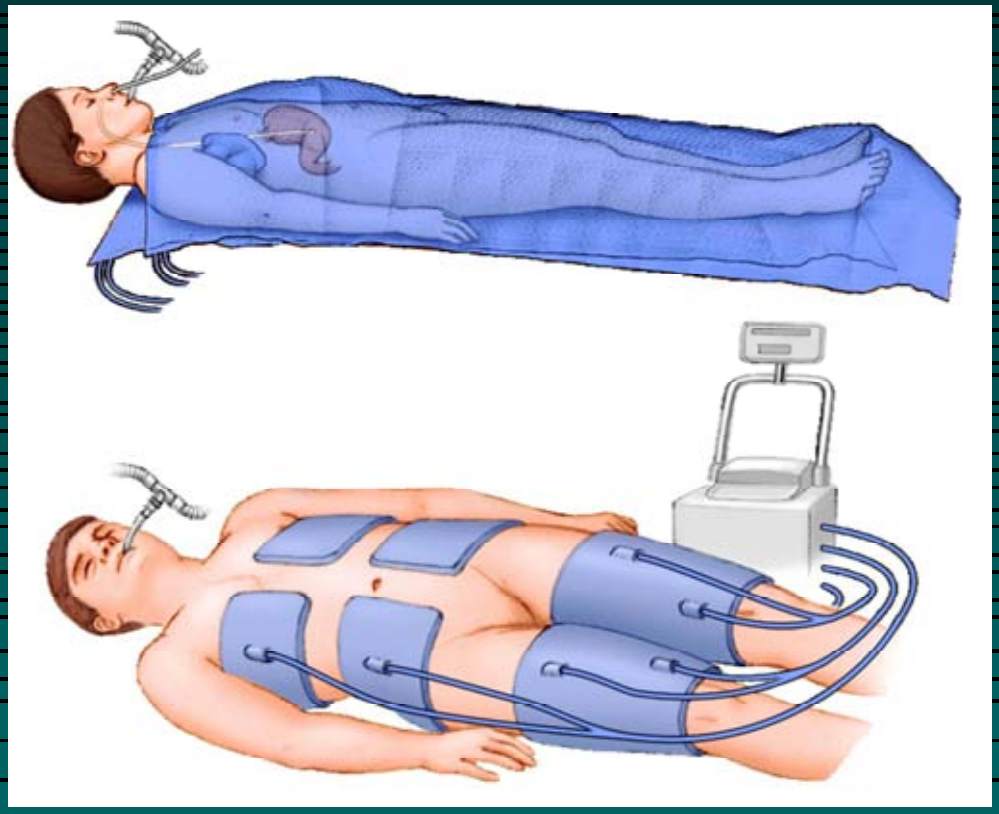
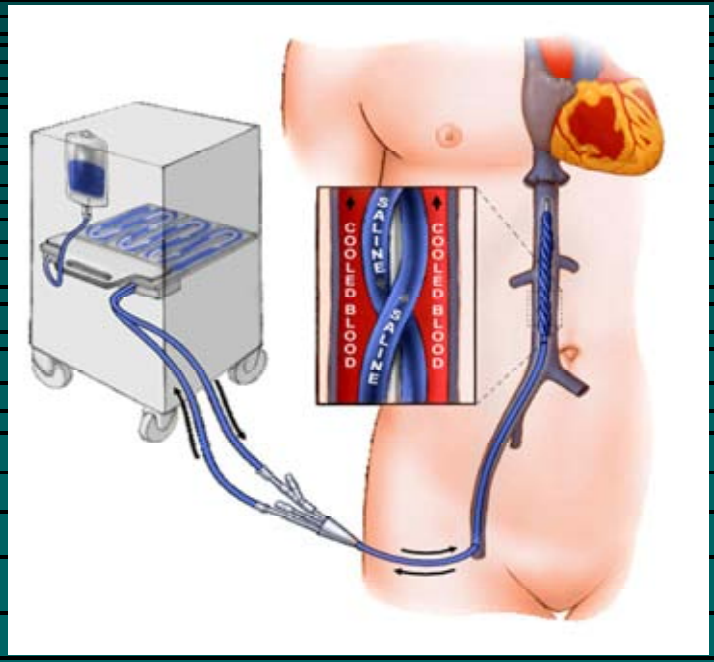
Induced Hypothermia and CPR





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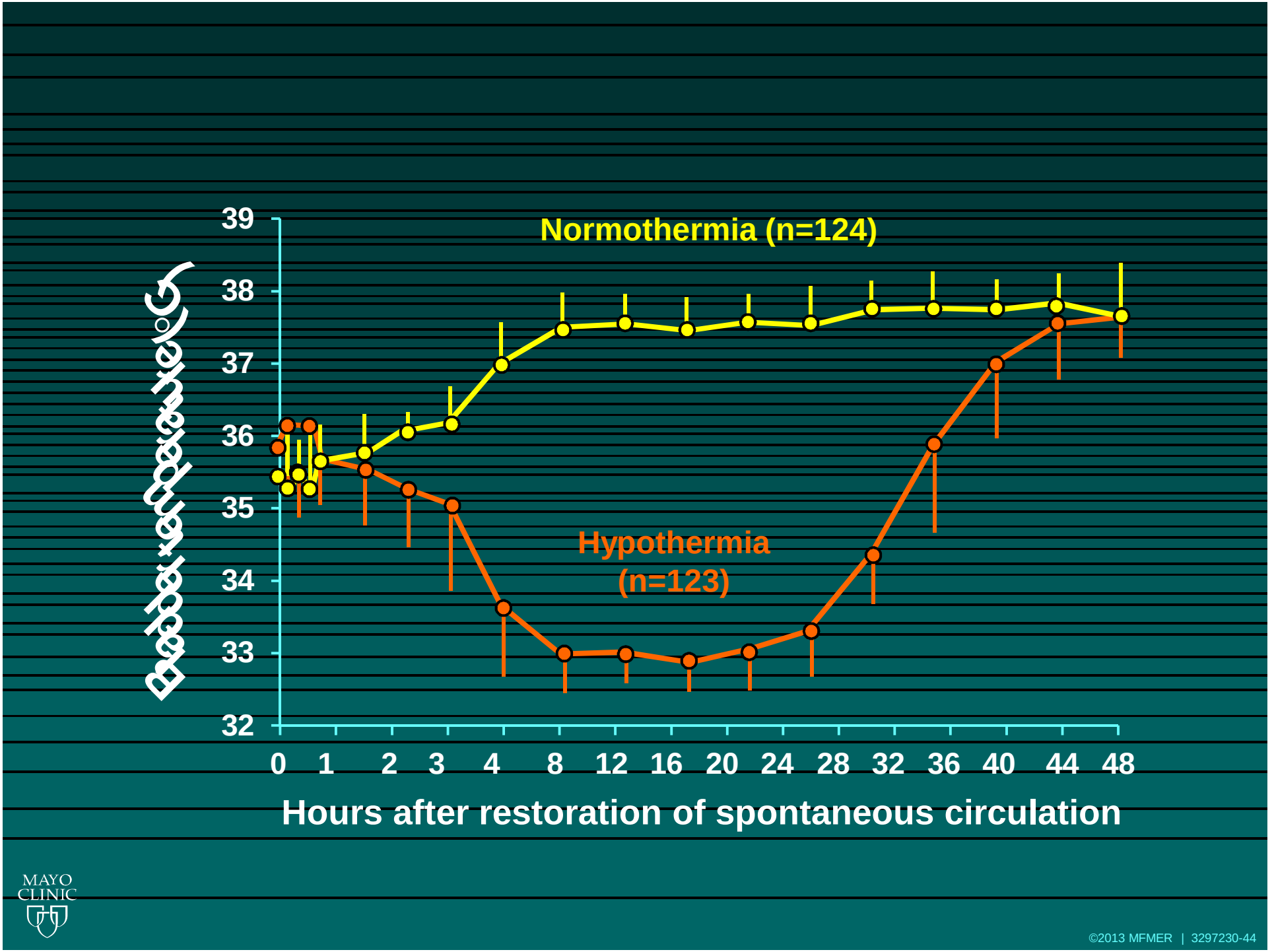

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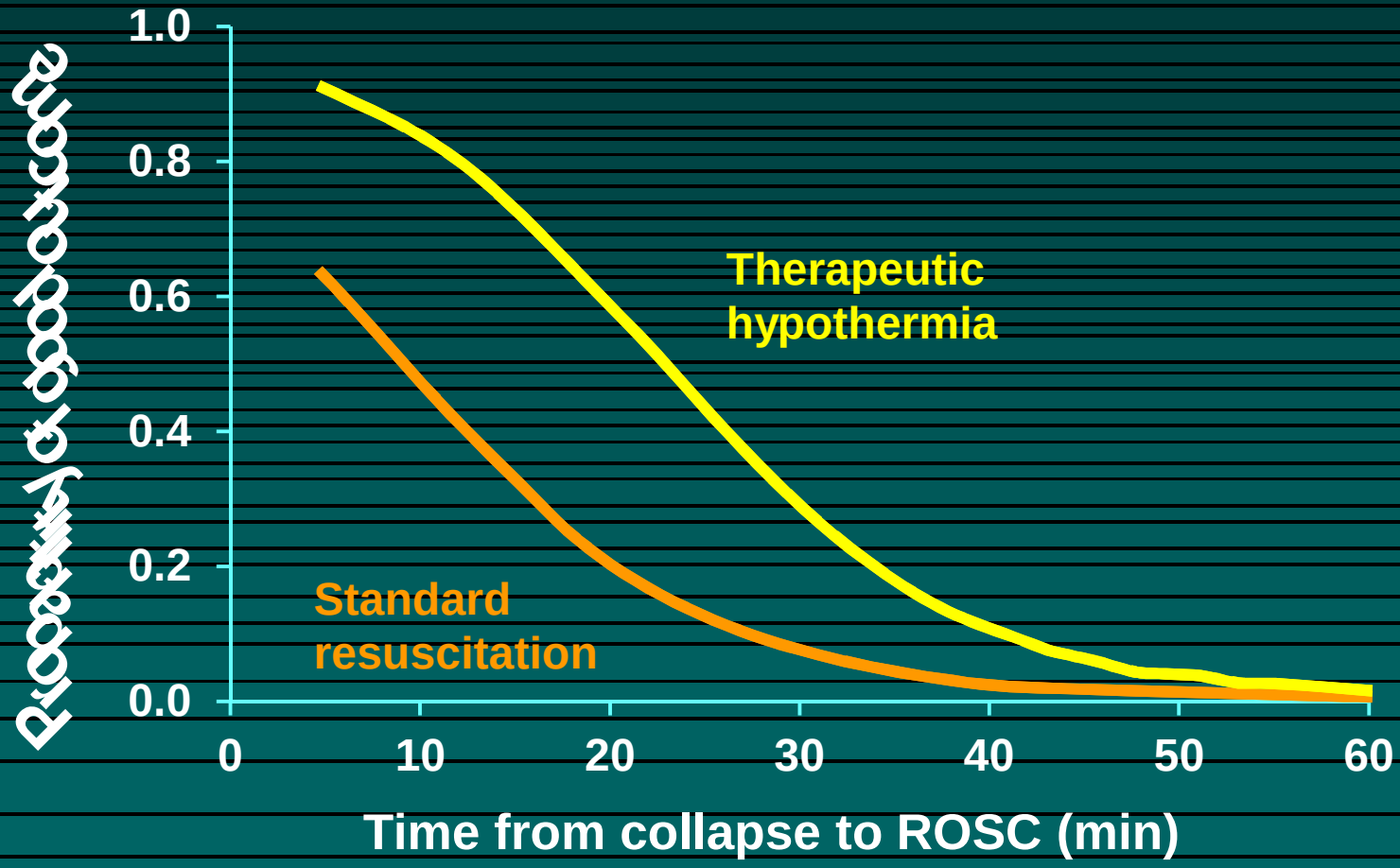
Time to Cooling Matters



Crit Care Med 34:1865, 2006

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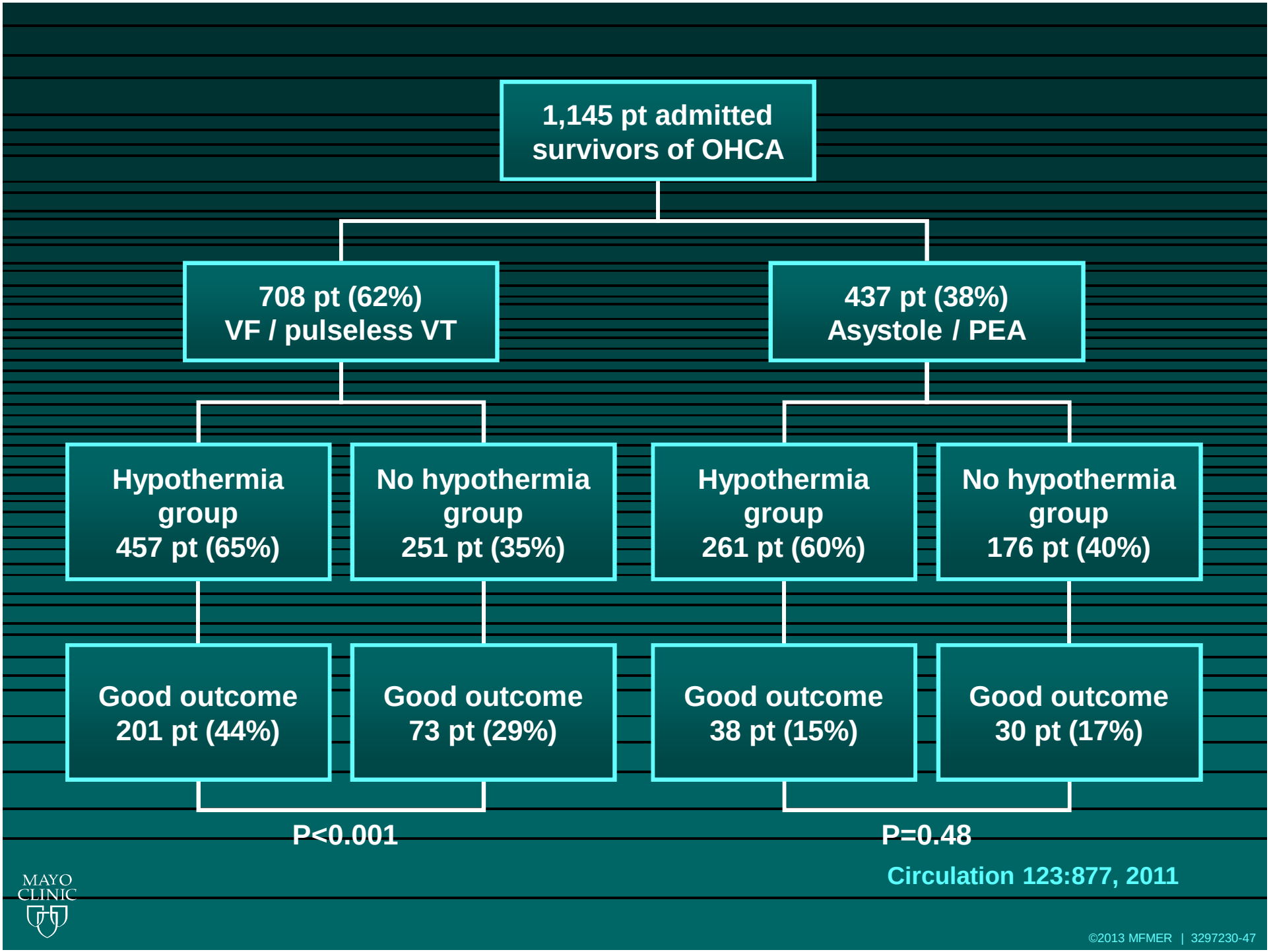

Circulation 123:877, 2011

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Therapeutic Hypothermia for All Patients?

- Data from 3 randomized controlled trials showed improvement neurologic outcome and survival at discharge
- Groups of patients with non-VF/VT as first cardiac rhythm did not show a statistically significant benefit
- Patients with a non-cardiac cause did not show a statistically significant benefit
- Patients with in-hospital cardiac arrest did not show a statistically significant benefit
- Patients with OHCA with VF/VT rhythms accounted for significant improvement in survival

Holzer AJ et al: The Cochrane Library: Issue 8, 2010

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BMJ

BMJ 2011;343:d5889 doi: 10.1136/bmj.d5889

HEAD TO HEAD

Does the evidence support the use of mild hypothermia after cardiac arrest? No

Several guidelines recommend hypothermia for comatose patients who have had a cardiac arrest outside hospital. **Jerry Nolan** and **Jasmeet Soar** (doi:10.1136/bmj.d5830) believe the data support this advice, but **Andrew Walden**, **Niklas Nielsen**, and **Matt Wise** question the quality of the evidence

Andrew P Walden *consultant in critical care medicine*[1], Niklas Nielsen *consultant in critical care medicine*[2], Matt P Wise *consultant in critical care medicine*[3]

[1]Intensive Care, Royal Berkshire Hospital, Reading, UK; [2]Department of Anaesthesiology and Intensive Care, Helsingborg Hospital, Helsingborg, Sweden; [3]Adult Critical Care, University Hospital of Wales, Cardiff CF14 4XW, UK

Historically, critical care physicians had a nihilistic approach towards patients who remained unconscious after a cardiac arrest outside hospital. This changed with the publication of two randomised clinical trials of mild induced hypothermia (32-34°C) that showed neuroprotection.[1 2] Subsequently this treatment has been embraced by the International Liaison Committee on Resuscitation, European Resuscitation Council, American Heart Association, and, most recently, the National Institute for Health and Clinical Excellence (NICE).

Animal models of cardiac arrest showed that mild hypothermia improved neurological outcome,[3] and these data were supported by small observational studies in patients. Clinical trials to determine whether this treatment benefited unconscious patients after cardiac arrest were therefore fitting. However, neither the above randomised trials[1 2] nor subsequent studies[4] provide sufficiently robust data to justify the conclusion that cooling to 32-34°C should be used after cardiac arrest outside hospital.

Evidence from clinical trials

A search for the terms "cardiac arrest" and "hypothermia" in PubMed identifies over 1800 publications since 2002, but they are almost all reviews, expert opinion, registries, and observational studies. Systematic review and meta-analysis, including a Cochrane review by Arrich and colleagues[5] concluded that mild hypothermia should be used after out of hospital cardiac arrest. Arrich and colleagues identified five published randomised trials, including one in abstract form,[1 2 4 6 7] and concluded that mild hypothermia was beneficial. However, the review did not rigorously evaluate the risks of random error, design flaws, and high risk of bias in these trials and failed to use the GRADE system[8] to assess evidence quality. This may have resulted in an overestimation of the treatment effect.

The largest clinical trial to date, undertaken by the Hypothermia After Cardiac Arrest Group,[2] recruited an average of just over one patient a week from nine centres over five years. Only 275 patients were randomised from 3551 screened, and this low inclusion rate of around 8% makes it difficult to generalise results to daily clinical practice. The study was discontinued because of slow recruitment and a lack of funding rather than because of defined stopping rules, and, importantly, there was no predefined power calculation. The level of coma before randomisation was not reported, and withdrawal of critical care was not standardised, introducing potential bias to the primary outcome measures of neurological outcome and death.[9]

The four other randomised clinical trials included in the Cochrane review also had methodological problems. Examples include quasirandomisation with odd and even dates,[7] early stopping without predefined rules,[4] unplanned adaptive design,[7] baseline differences between groups,[2 4 6 7] selective outcome reporting, and no description of sequence generation and allocation concealment[6 7] or blinding.[2 6 7] Reporting of adverse outcomes is also inconsistent, making it difficult to assess the harm from this treatment. Recognised adverse effects include increased risk of infection, haemodynamic instability, arrhythmias, coagulopathy, hyperglycaemia, and electrolyte abnormalities.[10 11] In one prospective observational registry based study of 765 patients treated with hypothermia after cardiac arrest outside hospital adverse events were common and included pneumonia (48%), electrolyte imbalance (37%), seizures (24%), arrhythmias (14%), bleeding (6%), and sepsis (4%).[11]

Recently Nielsen and colleagues[12] conducted a systematic review and meta-analysis of hypothermia after cardiac arrest and identified 478 patients from the same five trials[1 2 4 6 7] included in the Cochrane review.[5] They systematically evaluated the benefits and harms of the intervention, taking into account risk of systematic bias and random errors. Treatment effects were quantified using meta-analyses and trial sequential analysis,

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Target Temperature Management 33°C vs 36°C After Out-of-Hospital Cardiac Arrest

Scandinavian Critical Care Trials Group, Copenhagen Trial Unit, Copenhagen Denmark; Lund University, Lund Sweden (Clinical Trials NCT01020916)

“The accrued evidence is inconclusive and associated with risks of systematic error, design error and random error”

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Lingering concerns

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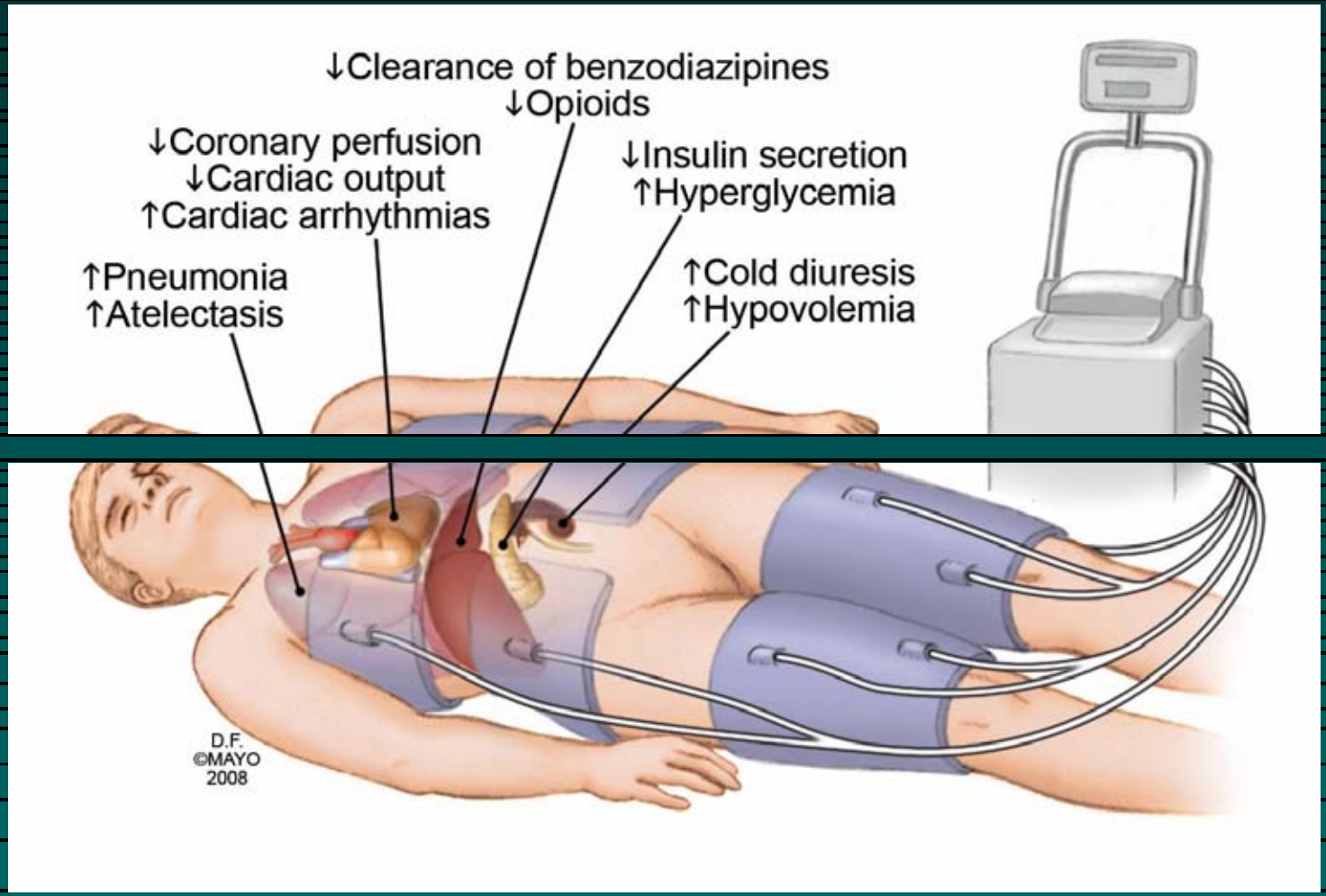

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1521-0081/41/1/214–223$25.00
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Effects of Hypothermia on the Disposition of Morphine, Midazolam, Fentanyl, and Propofol in Intensive Care Unit Patients

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ABSTRACT

Therapeutic hypothermia (TH) may induce pharmacokinetic changes that may affect the level of sedation. We have compared the disposition of morphine, midazolam, fentanyl, and propofol in TH with normothermia in man. Fourteen patients treated with TH following cardiac arrest (33–34°C) were compared with eight matched critically ill patients (36–38°C). Continuous infusions of morphine and midazolam were stopped and replaced with infusions of fentanyl and propofol to describe elimination and start of infusion pharmacokinetics, respectively. Serial serum and urine samples were collected for 6–8 hours for validated quantification and subsequent pharmacokinetic analysis. During TH, morphine elimination half-life ($t_{1/2}$) was significantly higher, while total clearance (CL_{tot}) was significantly lower (median [semi-interquartile range (s-iqr)]): $t_{1/2}$, 266 (43) versus 168 (11) minutes, $P < 0.01$; CL_{tot}, 1201 (283) versus 1687 (200) ml/min, $P < 0.01$. No significant differences were seen for midazolam. CL_{tot} of fentanyl and propofol was significantly lower in hypothermic patients [median (s-iqr)]: fentanyl, 726 (230) versus 1331 (678) ml/min, $P < 0.05$; propofol, 2046 (305) versus 2665 (223) ml/min, $P < 0.05$. Compared with the matched, normothermic intensive care unit patients, $t_{1/2}$ of morphine was significantly higher during TH. CL_{tot} was lower during TH for morphine, fentanyl, and propofol but not for midazolam. Reducing the infusion rates of morphine, fentanyl, and propofol during TH is encouraged

Introduction

Two pivotal studies have established the efficacy of treating comatose survivors of cardiac arrest with therapeutic hypothermia (TH) (33–34°C for 12–24 hours) (Bernard et al., 2002; Hypothermia after Cardiac Arrest Study Group, 2002; Peberdy et al., 2010). Patients treated with TH are given sedatives and analgesics to tolerate mechanical ventilation and to avoid shivering. Continuous infusions of morphine, fentanyl, midazolam, and propofol are among the most commonly used drugs for analgesia and sedation at the intensive care unit (ICU) (Payen et al., 2007).

Hypothermia can induce significant physiologic changes that affect drug disposition and action through changes in both metabolism and distribution (Kadar et al., 1982; Koren et al., 1987; Bansinath et al., 1988; Alcaraz et al., 1989; Beaufort et al., 1995; Leslie et al., 1995; Asokumar et al., 1998; Caldwell et al., 2000; Fukuoka et al., 2004; Tortorici et al., 2007; Arpino and Greer, 2008; Polderman, 2009). Reduced metabolism due to changes in enzyme activity during hypothermia may increase drug serum levels, and thus drug effects and duration of action (Polderman, 2004; Arpino and Greer, 2008). However, the effects of hypothermia on the activity of different enzymes vary; whereas 10°C lower temperature reduced cytochrome P450 (P450) activity on diazepam by 22%, conjugation of oxazepam was reduced by only 14% (Mortensen and Dale, 1995). In addition, whereas CYP3A and CYP2E activity as measured by clearance of midazolam and chlorzoxazone was approximately 50 and 60% lower in rats given cardiac arrest and TH compared with the control group, no differences were demonstrated for CYP2C/D (Zhou et al., 2011). This substrate specificity implies that the effects of hypothermia on pharmacokinetics (PK) may vary between drugs (Mortensen and Dale, 1995; Zhou et al., 2011; Zhou and Poloyac, 2011).

Morphine is metabolized by uridine diphosphate glucuronosyltransferase 2B7 (UGT2B7), but to our knowledge, no studies on the effect of hypothermia on isolated UGT2B7 exist. In animals, reduced glucuronidation and increased serum concentrations are consistent with results from neonates, who had approximately 40% higher serum concentrations and 23% reduced clearance at 33–34°C compared with

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Parts of the morphine and midazolam data were presented at the European Society of Intensive Care Medicine 21st Annual Congress; 2008 Sept 21-24; Lisbon, Portugal at the annual meeting of the Norwegian Society of Anaesthesiology 2008; and at the annual winter meeting of the Norwegian Society of Pharmacology and Toxicology 2009. An updated abstract was presented at the 31st Congress of the Scandinavian Society of Anaesthesiology and Intensive Care Medicine 2011, Bergen, Norway. This article will be included in the Ph.D. thesis *Pharmacological Aspects of Therapeutic Hypothermia* (Bjelland TW).

This study was carried out in accordance with the Declaration of Helsinki.

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ABBREVIATIONS: Cal, calibration standard; CL_{tot}, total clearance; CL_R, renal elimination clearance; C_{SS}, steady-state concentration; GCS, Glasgow Coma Scale; ICU, intensive care unit; IS, internal standard, λ_z, elimination rate constant; LOQ, limit of quantification; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; MAAS, Motor Activity Assessment Scale; MAP, mean arterial pressure; MP, mobile phase; OH-midazolam, α-hydroxy-midazolam; P450, cytochrome P450; PK, pharmacokinetic(s); QC, quality control; SAPS II, Simplified Acute Physiology Score II; s-iqr, semi-interquartile range; T_0, start of the pharmacokinetic study period; TH, therapeutic hypothermia; UGT2B7, uridine diphosphate glucuronosyltransferase 2B7.

Estimates in Clearance Change in Drugs Used in Hypothermia for Cardiac Arrest

	Percent per 1°C decrease
Midazolam	11
Remifentanil	6.3
Vecuronium	11.3
Fentanyl	6
Propofol	8

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Prognostication after Cardiac Arrest and Hypothermia
A Prospective Study

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Objective: Current American Academy of Neurology (AAN) guidelines for outcome prediction in comatose survivors of cardiac arrest (CA) have been validated before the therapeutic hypothermia era (TH). We undertook this study to verify the prognostic value of clinical and electrophysiological variables in the TH setting.
Methods: A total of 111 consecutive comatose survivors of CA treated with TH were prospectively studied over a 3-year period. Neurological examination, electroencephalography (EEG), and somatosensory evoked potentials (SSEP) were performed immediately after TH, at normothermia and off sedation. Neurological recovery was assessed at 3 to 6 months, using Cerebral Performance Categories (CPC).
Results: Three clinical variables, assessed within 72 hours after CA, showed higher false-positive mortality predictions as compared with the AAN guidelines: incomplete brainstem reflexes recovery (4% vs 0%), myoclonus (7% vs 0%), and absent motor response to pain (24% vs 0%). Furthermore, unreactive EEG background was incompatible with good long-term neurological recovery (CPC 1–2) and strongly associated with in-hospital mortality (adjusted odds ratio for death, 15.4; 95% confidence interval, 3.3–71.9). The presence of at least 2 independent predictors out of 4 (incomplete brainstem reflexes, myoclonus, unreactive EEG, and absent cortical SSEP) accurately predicted poor long-term neurological recovery (positive predictive value = 1.00); EEG reactivity significantly improved the prognostication.
Interpretation: Our data show that TH may modify outcome prediction after CA, implying that some clinical features should be interpreted with more caution in this setting as compared with the AAN guidelines. EEG background reactivity is useful in determining the prognosis after CA treated with TH.

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Following resuscitation from cardiac arrest (CA), 40 to 60% of patients recover spontaneous circulation.[1] Prior to the use of therapeutic hypothermia (TH), most survivors sustained anoxic brain damage,[2,3] and only about 20% survived to discharge.[4] The global success rate for out-of-hospital CA has thus been <10%,[5] and those remaining comatose may suffer from severe cognitive impairment and long-term disability, placing great psychological and financial burdens on family and society.[6]

For many years, neurological examination and electrophysiological studies have guided physicians in predicting outcome of patients with coma after CA. However, clinical and electroencephalographic (EEG) prognostic markers were developed before the introduction of TH, as were recent guidelines of the American Academy of Neurology (AAN) for outcome prediction of comatose survivors of CA.[7] Randomized clinical trials have shown that TH improves survival and neurological recovery in comatose survivors of CA,[8,9] and has therefore been recommended as a standard of care.[10] Therefore, additional studies are needed to more precisely assess the prognostic value of each component of the AAN clinical and electrophysiological practice parameters, and determine whether they are still applicable in the setting of TH.[7,11] We therefore prospectively evaluated a large cohort of comatose adult patients successfully resuscitated from CA

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Prognostication after TH not perfect

- Myoclonus status — FPR 3%
- Absent motor — FPR 24%
- More than one BSR absent — FPR 4%
- Unreactive EEG — FPR 7%
- Absent SSEP — FFR 0%

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Prognostic Factors

- Absent N20 SSEP (during or after TH)
- NSE may be useless
- Absent pupils and corneal reflexes
- Non reactive EEG after rewarming
- Seizures during hypothermia
- Myoclonus and status epilepticus

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Summary

- TH may improve outcome in some patients
- Still enormous devastation and mortality
- Prognostication after TH is very difficult due to confounders
- Better understanding pharmacokinetics is needed

New Challenges for the Neurologist !

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