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Early prognostication of outcome after cardiac arrest

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Cardiac arrest

Background 1: overview

- Sucessful ROSC: 11%-15% Stiell *NEJM* 2004
- Consciousness recovery after ICU admission: 13%-41%

  Bassetti *JNNP* 1996, Zandbergen *Neurology* 2006, Oddo *CCM* 2006
- Overall survival after cardiac arrest: <5% Stiell *NEJM* 2004
- Long-term:memory impairment, independent Mateen *Neurol* 2011

→How to predict <u>good outcome</u>? (1- death or PVS)

→How to predict <u>bad outcome</u>? (death or PVS)

Background 2: epidemiologic ratios

	Bad outcome	Good outcome
Test +	A	**B**
Test -	C	D

Sensitivity = A /A+C

Specificity = D /B+D

PPV = A /A+B

NPV = D /C+D

- Sens / Spec = test dependent
- PPV / NPV = prevalence dependent

Background 2: epidemiologic ratios

	Bad outcome	Good outcome
Test +	A	**B**
Test -	C	D

Sensitivity = A /A+C

Specificity = D /**B**+D

PPV = A /A+**B**

NPV = D /C+D

Aim: -PPV for bad outcome = 100%

-FPR (1-specificity) = 0%

Background 3: myoclonus Hallett *Mov Dis* 2000

- Acute PH myoclonus: brainstem or cortical

  →possible epileptiform activity on EEG

- Chronic PH myoclonus Lance & Adams *Brain* 1963: cortical

  →frequent epileptiform activity on EEG

- Role of curarisation for evaluation
- Continuum is possible: *acute →chronic*

AAN Guidelines

CAVE: hypothermia !!!

- Not considered in the AAN guidelines
- May modifiy prognostication

Young *NEJM* 2009, Josephson *Ann Neur* 2010, Samaniego *Curr N Neurosci Rep* 2010

CHUV: hypothermia since 2004

- Improves outcome, **NNT ~7** Bernard *NEJM* 2002, HACASG *NEJM* 2002

Methods:

•Mild hypothermia to 33°C for 24h

•External cooling

•MDZ 0.1 mg/kg/h, fentanyl 1.5 μg/kg/h, vecuronium

Risks Holzer *NEJM* 2010

•Overall: 1%

•Bleeding, DVT, infection, pulm edema, electrolyte imbalance

Clinical history

AAN Rogove *CCM* 1995, Zeiner *Arch Int Med* 2001

- Anoxia time
- Type of cardiac rhythm (FV vs. A or PEA)
- Time to ROSC

- All are independent predictors
- PPV insufficient
- **Level B**

Neurological examination

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- Myoclonus <24h = PPV 100%

  Wijdicks *Ann Neurol* 1994, Zandbergen *Neurology* 2006

- Motor GCS ≤ 2 after 72h = PPV 100%

  Zandbergen *Neurology* 2006

- No pupill. reaction > 24-72h = PPV 100%

  Zandbergen *Neurology* 2006

- No corneal, oculoceph. reflexes >72h = PPV 100%

  Zandbergen *Neurology* 2006

- **Level B**

Hypothermia (FPR)

- Motor: 14% (recovery at 6 d); Pupils: 0% (37 pts)

  Al Thenayan *Neurology* 2008

- Motor: 24%; Brainstem-R: 4%; Myoclonus 3% (111 pts)

  Rossetti *Ann Neurol* 2010

- Motor: 12% (sedation); Pupils: 0%; Myoclonus: 0% (54 pts)

  Samaniego *Neurocrit Care* 2010

- Motor: 10% ; Pupils: 1%; Corneal: 4% (391 pts)

  Bouwes *Ann Neurol* 2012

Summary

- Hypothermia /sedation delay motor recovery
- Motor signs not reliable
- Brainstem reflexes and myoclonus « more » reliable

Serum markers

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- NSE > 33µg/l after 24-72h = PPV 100%

  Zandbergen *Neurology* 2006

- **Level B**

Hypothermia: NSE

- >33µg/l : FPR 0% (90 pts) Oksanen *Resuscitation* 2009
- >28µg/l : FPR 0% (102 pts) Rundgren *Resuscitation* 2009
- >33µg/l : FPR 29%! (74 pts) Fugate *Ann Neurol* 2010
- >78µg/l : FPR 0% (vs. >27µg/l for normothermic)

  Steffen *Crit Care* 2010
- >81µg/l : FPR 0% (310 pts) Bouwes *Ann Neurol* 2012
- >97µg/l : FPR 0% (97 pts) Daubin *BMC Cardiovasc Dis* 2011
- CAVE: laboratory and hemolysis!

<u>Summary</u>

- Hypothermia may rise cutoffs !

Electroencephalography

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- EEG generalized suppression, spontaneous burst-suppression, PEDs on flat background = PPV 95%

  Bassetti *JNNP* 1996, Young *Neurocrit Care* 2005
- **Level C**

Awakening after PSE Rossetti *Neurology* 2009

- 3/107 pts retrospectively; 3/74 prospectively

All 6 survivors: reactive EEG, preserved brainstem reflexes and SSEP

Hypothermia: EEG

- 30% postanoxic SE (PSE) post hypo-T Rossetti *Ann Neurol* 2010
- PSE ≠ death (FPR 9%), survivors (~10% of PSE) show reactive EEG, preserved N20 and brainstem-reflexes

  Rossetti *Neurology* 2009, *Ann Neurol* 2010
- Otherwise, bad outcome (FPR 0%)

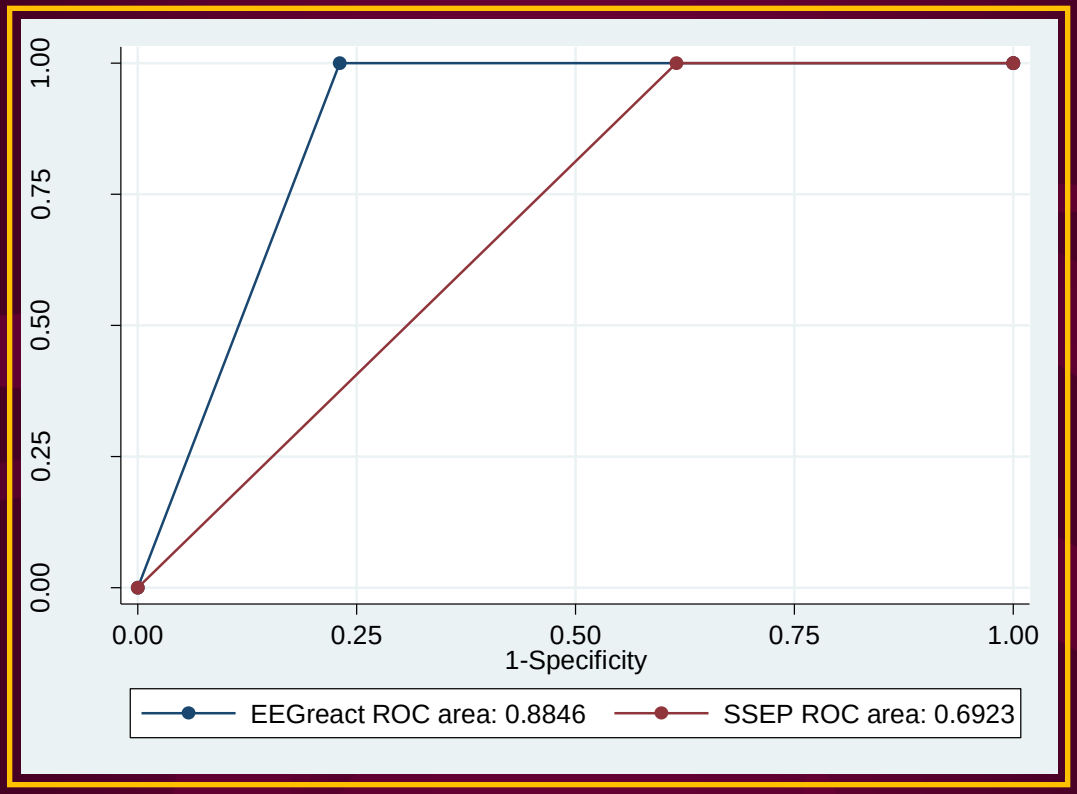
  Fugate *Ann Neurol* 2010, Thomke *Neurology* 2010
- Baseline EEG non-reactivity (FPR 7%-9%)

  Rossetti Ann Neurol 2010, Al Thenayan *J Crit Care* 2010

PSE survivor: Video-EEG

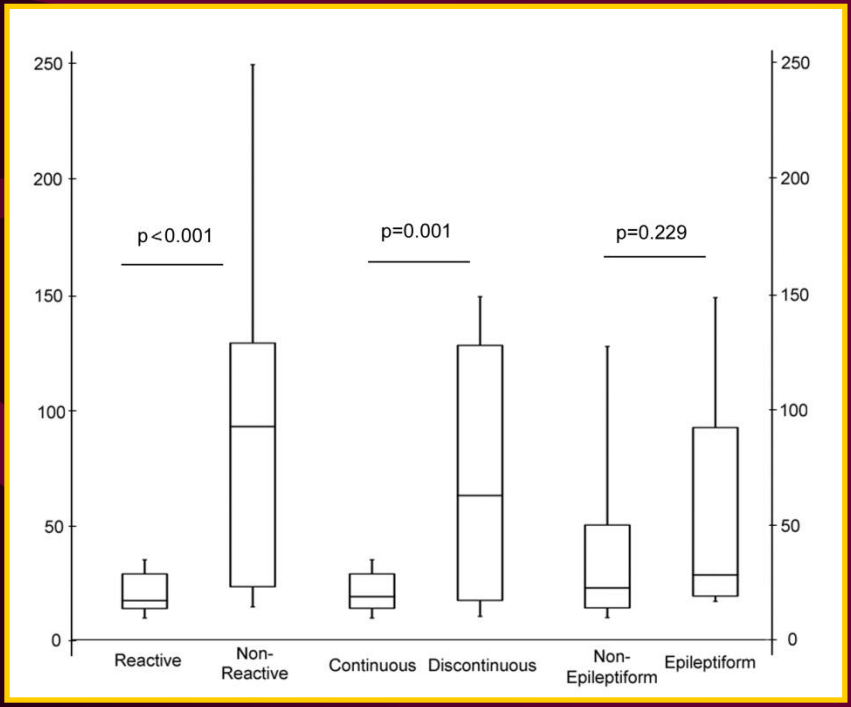
Acute Chronic

cEEG during hypothermia (34 pts) Rossetti *Crit Care* 2010



cEEG during hypothermia (61 pts) Rossetti *Neurology* 201

	CPC 1-2 (28 patients)	CPC 3-5 (33 patients)
EEG unfavorable features (during hypothermia)		
a-Non reactive background	0	23 (70%)
b-Discontinuous background (burst-suppression)	2 (7%)	26 (79%)
c-Epileptiform transients +	0	10 (30%)
-Sum of EEG unfavorable features (a-c): median, range*	0 , 0 – 1	2 , 0 – 3



Spearman's rho = 0.45; p<0.001

Hypothermia: cEEG / aiEEG

- 19 children: 32% SE (nonconvulsive) Abend *Neurology* 2009
- 51 adults: 10% SE (all died) Legriel *Neurocrit Care* 2009

- 30 adults: BS-ratio, entropy (FPR 19%-29%)

  Wennevirta *CCM* 2009
- 95 adults: BS pattern (FPR 0%), SE (FPR 4%)

  Rundgren *CCM* 2009

<u>Summary</u>

- Nonreactive EEG (especially during hypoth.) seems reliable
- PSE not invariably related to death

Somatosensory evoked potentials

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- SSEP with bilat. absent N20 (>24h) = PPV 100%

  Zandbergen *Neurology* 2006

- **Level B**

- MLAEP, MLSSEP, MMN: **Level U**

Hypothermia (absent N20, FPR)

- FPR 2% (112 pts) Leithner *Neurology* 2010
- FPR 0% (also sedated, 46 pts) Samaniego *Neurocrit Care* 2010
- During HypoT : FPR 3% (263 pts) , After HypoT: FPR 0% (128 Pts) Bouwes *Ann Neurol* 2012
- FPR 0% (with other bad predict., 95 pts) Rossetti *Ann Neurol* 2010

Summary

- Very (but not absolutely?) reliable
- Poor prediciton of good outcome
- Cognitive EP (MMN Fischer *CCM* 2006) ?

Imaging

AAN Torbey *Stroke* 2000, Wijdicks *AJNR* 2001

- CT (edema) and MRI (hyperintensity on DWI, FLAIR)
- **Level U**

Hypothermia

Quantitative ADC analysis

Wijman *Ann Neurol* 2009

- >10% brain volume with < 650 x 10^{-6} mm^2/sec at 2-5 days (FPR 0%)
- Higher sensitivity than neurological examination

Hypothermia

- Time dependency (false negative at <24h)

  Wijman *Ann Neurol* 2009, Mlynash Stroke 2010

Summary

- Quantitative imaging (>24h) promising
- Need of further studies

To summarize…

- 111 patients treated with TH, prospective Rossetti *Ann Neurol* 2010
- EEG reactivity not used for decisions

  (self-fulfilling-prophecy Zandbergen *Neurology* 2006)

TABLE 2: Variables Predicting Death after Cerebral Anoxia

Variable	FPR
Non-VF CA (asystole or PEA)	0.15 (0.06–0.29)
ROSC >25 minutes	0.24 (0.13–0.40)
≥1 brainstem reflexes absent[a]	0.04 (0.01–0.15)
Motor response worse than flexion	0.24 (0.13–0.40)
Early myoclonus	0.03 (0.00–0.11)
Epileptiform activity on first EEG	0.09 (0.02–0.21)
Unreactive EEG background	0.07 (0.01–0.18)
Bilaterally absent N20 on SSEP	0.00 (0.00–0.08)

TABLE 3: Prognostic Value for In-Hospital Mortality (Presence of 2 or More Variables among Bilaterally Absent SSEP, Unreactive EEG Background, Early Myoclonus, and Incomplete Recovery of Brainstem Reflexes)

Sensitivity	0.79 (95% CI, 0.67–0.88)
Specificity	1.00 (95% CI, 0.92–1.00)
Positive predictive value	1.00 (95% CI, 0.93–1.00)
Negative predictive value	0.76 (95% CI, 0.63–0.86)
Unweighted accuracy	0.90

Interdisciplinary & multimodal :

Care withdrawal if

- Brain death (clinical diagnosis, apnea test), or
- At >48hours, at least 2 of
  - early myoclonus
  - absent of 1 or more brainstem reflexes at 72h
  - flat or nonreactive EEG (normo- and hypothermia?)
  - bilaterally absent N20 (normo- and hypothermia?)

Unclear roles for NSE, imaging

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