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Clinical paper

Post resuscitation prognostication by EEG in 24 vs 48 h of targeted temperature management

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Abstract

Objective: To test if prognostic performance is affected by prolonged targeted temperature management (TTM) in comatose out-of-hospital cardiac arrest patients using two recently proposed EEG pattern classification models.

Methods: In this sub-study of the *"Target Temperature Management for 48 vs. 24 hand Neurologic Outcome after Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial"*, EEGs of 20–30 min duration were collected 24 h and 48 h after reaching the target temperature of 33 ± 1 °C. We classified EEGs according to two EEG classification models by Westhall et al. ("highly malignant", "malignant" and "benign") and Hofmeijer et al. ("unfavorable", "intermediate" and "favorable"). We tested prognostic ability against 6 months functional outcome using the Cerebral Performance Category score.

Results: We recorded EEGs in 120 patients at 24 h and in 44 patients at 48 h. We found no difference in specificities or sensitivities of the two models between the two TTM groups (all p-values >0.19) or in prognostication at 24 h compared to 48 h (all p-values >0.13), except for the presence of EEG reactivity favoring prognostication at 24 h ($p < 0.001$). Being classified in the "benign" or "favorable" category was strongly associated with good outcome with specificities of 100% (90–100) and 97% (85–100) for the Westhall and Hofmeijer models respectively.

Conclusions: We found no difference in the prognostic performance of the two studied EEG classification models during prolonged TTM for 48 h compared to standard duration, nor between EEG classification performed at 24 h versus 48 h after reaching target temperature. The two models performed best in good outcome prediction.

Keywords: Targeted temperature management, Prolonged targeted temperature management, Cardiac arrest, Post-resuscitation care, Prognostication, Electroencephalography (EEG)

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https://doi.org/10.1016/j.resuscitation.2018.10.035

Received 5 September 2018; Received in revised form 30 October 2018; Accepted 30 October 2018

Introduction

Out-of-hospital cardiac arrest (OHCA) affects an estimated 400,000 people in Europe each year.[1] Survival rates are approximately 10% in overall survival and 50%[2] in patients admitted to the intensive care unit (ICU). Post-resuscitation care in the ICU includes target temperature management (TTM) to 32–36 °C for at least 24 h, but optimal depth[3] and duration[3] is still subject to research and discussion.

The most common cause of death in the ICU after OHCA, is hypoxic-ischemic encephalopathy, accounting for 60–70% of deaths.[6–8] Further, 2–4% of survivors have serious neurologic deficits.[3,4]

Timely and correct prognostication is of vital importance, both to avoid self-fulfilling prophecies and to guide physicians in decisions on withdrawal of care. EEG is an important prognostic tool and also recommended for ruling out subclinical seizures.[5] However, inter-rater variability[6] and the confounding effects of sedation and TTM together with the variety of classification systems makes it difficult to define optimal use of EEG for prognostic purposes.[7] It is important to study the effects of TTM on EEG patterns in order to understand how to refine prognostication and evaluate possible treatment effects of different TTM regimens. The aim of the present study was to investigate the impact of prolonged TTM on prognostic performance and EEG evolution over time, using two recently proposed EEG pattern classification models; the Hofmeijer model[8] and the Westhall[9] model, following the standardized EEG terminology proposed by the American Clinical Neurophysiology Society (ACNS).[10]

Methods

Patients

The present study is a sub-study of the *"Targeted Temperature Management for 48 vs. 24 h and Neurologic Outcome After Out-of-Hospital Cardiac Arrest: A Randomized Clinical Trial"* (the TTH48 trial)[3] involving the 159 patients enrolled in the ICUs at Aarhus University Hospital, Denmark, and Stavanger University Hospital, Norway. The inclusion criteria of the TTH48 trial were the following: OHCA with a presumed cardiac origin, Glasgow Coma Scale below 8, sustained spontaneous circulation after resuscitation (no need for cardiac compressions for 20 min and clinical signs of circulation), age between 18 and 80 years and time from cardiac arrest to initiation of cooling less than 4 h. Exclusion criteria are listed in the TTH48 study protocol.[11]

Either surface or intravascular feedback cooling systems were employed to maintain a target temperature (TT) of 33 ± 1 °C. The body core temperature was continuously monitored in the urinary bladder, and maximal rewarming rate was 0.5 °C h^{-1}. Included patients were sedated following an identical sedation protocol between groups with intravenous infusions of propofol/midazolam and remifentanil/fentanyl until normothermia was reached. Clinical data were collected using the patients' medical records. Prehospital cardiac arrest data were collected according to the Utstein guidelines.[12] The study was approved by the Danish Data Protection Agency and the Central Denmark Region Committee on Health Research Ethics (number 20110022) and the Regional Ethics Committee of Western Norway (ref 2013/1486).

EEG recordings

Patients eligible to an EEG recording were comatose patients included in the TTH48 trial. EEGs were recorded at two time intervals measured from time of TT; at 24 h (from 12 to 24 h) when all patients were hypothermic and at 48 h (from 36 to 48) when TTM48 patients were hypothermic and TTM24 patients were normothermic. For all recordings, 19 electrodes were used according to the international 10/20 system in a common average reference montage including Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, Pz, P3, P4, T5, T6, O1, and O2. Prefrontal and occipital electrodes were not included in the average reference. Band-pass filter was 0.5–70 Hz and electrode impedances were kept below 5 kΩ. Sampling rate was 256 samples/sec. In Aarhus the "Nicolet One" software from "Natus" version 5.82 was used to record, store and analyse EEG data and in Stavanger the "Galileo NT PMS" version 3.80. Duration of EEG recordings where 20–30 min.

Stimulation protocol

A standardized protocol including six 30 s stimulation epochs with a minimum of two minutes between stimulations was used. Four noxious stimulations were performed; two using pen-pressure on the side of the nail-bed of a finger of both upper extremities, one applied on a toe of one lower extremity and one sternal massage. Force was applied until whitening of surrounding tissue, and sternal massage was applied in a twisting motion in order not to cause EEG-artefacts from head movements. The fifth and the sixth stimulations were manual eye opening and auditory stimulation by key rattling.

In all EEGs, the six stimulation epochs of 30 s were marked with annotations and controlled by video. EEGs were recorded by research personnel, or experienced physicians and technicians.

EEG evaluation

A traditional and blinded evaluation of the EEGs, including assessment of continuity and visual evaluation of EEG reactivity was performed by a specialist in neurophysiology (Birger Johnsen). EEG patterns were classified according to two models:

1. The Westhall model[9]

a) "highly malignant" (suppression, suppression with periodic discharges, burst suppression)
b) "malignant" (malignant periodic or rhythmic patterns, discontinuous background activity, low-voltage background, reversed anterior-posterior gradient or nonreactive background)
c) "benign" (absence of above mentioned "malignant" or "highly malignant" features).

2. The Hofmeijer model[8]

a "unfavorable" (isoelectric, low-voltage, burst-suppression with identical bursts)
b "intermediate" (evolving seizures, generalized periodic discharges (GPDs), or burst-suppression without identical bursts)
c "favorable" (continuous patterns, either diffusely slowed, or normal)

EEG reactivity was measured specifically and classified as "not present" or "present", if in doubt it was classified as "present". EEGs

with discontinuous background activity or rythmic delta activity were not considered in the Hofmeijer model. We assigned these two patterns to the "intermediate" category in the present study.

SSEP recordings

SSEPs were recorded on Dantec Keypoint.Net version 2.33. Repetitive stimuli were delivered unilaterally on both sides over the median nerve at the wrist with a stimulation frequency of three Hz and an intensity sufficient to produce thumb twitching. Recordings were peripheral at Erb's point, at spinal level over C7 referred to Fz of the international 10–20 system, and over the contralateral cortex 1.5 cm posterior to C3/C4 referred to Fz. Band-pass filters were 100–2000 Hz for the peripheral recording and 10–3000 Hz for the spinal and cortical recordings. Responses were averaged until reproducibility, at least 250 stimulations.

Outcome measure

Neurological outcome was evaluated using the cerebral performance categories (CPC) scale after six months. CPC 1 is no neurological deficit, CPC 2; mild to moderate dysfunction, CPC 3; severe dysfunction requiring help for activities of daily living, CPC 4; coma, and CPC 5; death. Neurological outcome was dichotomised such that a CPC score of 1–2 was considered a good outcome and a CPC score of 3–5 a poor outcome.

Prognostic performance between TTM groups include specificity, sensitivity (primary hypothesis), positive predictive value (PPV) and negative predictive value (NPV) of the two EEG classification models Westhall and Hofmeijer.

Statistical analysis

Baseline characteristics were presented as medians and interquartile ranges for continuous data and as counts and percentages for categorical data, analysed using Mann Whitneys and chi square test respectively. Specificities and sensitivities of EEG categories were compared by the Fischers exact test or chi squared test when appropriate. Mc Nemars test was used in the comparison of specificity and sensitivity between paired patients from 24 h to 48 h.

Results

We recorded 120 EEGs at 24 h (Fig. 1), median hours from TT to EEG; 20 h (IQR: 16–23, range: 8–36) and median hours from cardiac arrest to EEG; 25 h (IQR: 21–28, range: 14–40). In 44 of these patients, we also recorded EEGs at 48 h, median hours from TT to EEG; 43 h (IQR: 38–46, range: 25–65) and median hours from cardiac arrest to EEG; 49 h (IQR: 43–53, range: 31–68). We found no differences between TTM groups in time from cardiac arrest to TT or cardiac arrest to EEG (all p-values above 0.16). We found no difference between TTM groups at the 6-month follow-up in neurological outcome or baseline characteristics (Table 1). Due to recurrent technical issues, SSEPs were not recorded on all patients. Eighty-six SSEPs were performed at 24 h and 26 recordings at 48 h.

Prognostication at 24 h

For both models, there was no difference in specificities or sensitivities of the EEG categories between TTM groups at 24 h (Table 2). Comparing the two models on all 120 patients, we found a significantly higher sensitivity in the Westhall "highly malignant" category compared to the Hofmeijer "unfavorable" category ($p = 0.01$, data not shown).

Westhall: Of the 27 patients with a "highly malignant" pattern at 24 h, eight had a good outcome (CPC 1 or 2) with five in the TTM24 group and three in the TTM48 group. A "benign" EEG at 24 h was highly predictive of a good outcome (Table 3).

Hofmeijer: Three EEGs were classified as "unfavorable", all with poor outcome. A "favorable" EEG at 24 h was highly predictive of a good outcome (Table 3).

Both models performed well in the prediction of good outcome at 24 h with PPVs at 100% and 98% for Westhall and Hofmeijer, respectively. As single predictor, presence of reactivity at 24 h had a PPV of 96% (Table 3).

Absence of SSEP at 24 h had a specificity of 100% for prediction of poor outcome with a sensitivity of 23%.

Prognostication at 48 h

We found no significant differences between TTM groups in specificities or sensitivities at 48 h. There was a near-significant

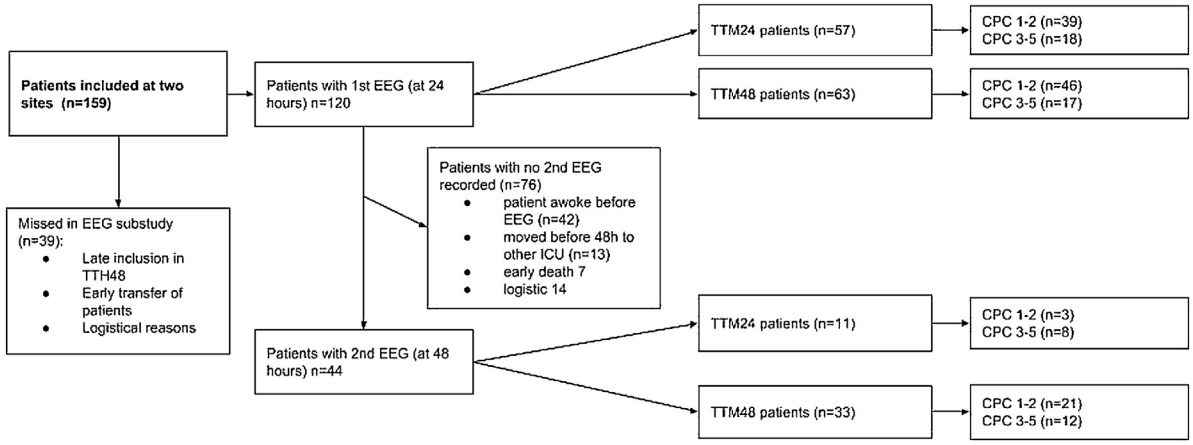

Fig. 1 – Flowchart of recorded and missing EEGs. TTM24 = targeted temperature management for 24 h. TTM48 = targeted temperature management for 48 h. CPC = cerebral performance categories.

Table 1 – Baseline characteristics.

	Included patients	TTM24	TTM48		Missed inclusion	
	n (%)	n (%)	n (%)	p-Value	n (%)	p-Value
Patients	120 (100)	57 (48)	63 (53)		39 (100)	
Age, years (median and IQR)	60 (53–68)	59 (51–67)	60 (53–70)	0.82	66 (59–70)	0.09
Male	107 (89)	52 (91)	55 (87)	0.49	33 (85)	0.45
Bystander CPR performed	105 (88)	50 (88)	55 (87)	0.94	37 (95)	0.20
Primary shockable rhythm	104 (87)	47 (82)	57 (90)	0.23	35 (90)	0.74
Time to ROSC, minutes (median and IQR)	20 (15–29)	20 (14–27)	20 (15–30)	0.54	21 (14–29)	0.67
PCI performed	52 (43)	25 (44)	27 (43)	0.90	17 (44)	0.64
Previous AMI	18 (15)	10 (18)	8 (13)	0.46	11 (28)	0.06
Neurological outcome (CPC)						
Good outcome	85 (71)	39 (68)	46 (73)	0.58	25 (64)	0.43
Poor outcome	35 (29)	18 (32)	17 (27)		14 (36)	

TTM24 = targeted temperature management for 24 h. TTM48 = targeted temperature management for 48 h. ROSC = return of spontaneous circulation. CPC = cerebral performance categories outcome scale. AMI = acute myocardial infarction. CPR = cardio pulmonary resuscitation. IQR = inter quartile range. Missed inclusion are the patients randomized in the main TTH48 trial but not included in the present substudy. P-values for difference between TTM-groups are presented as well as p-values for difference between included and missed patients.

Table 2 – Prediction of outcome by two EEG classifications based on 120 EEGs at 24 (upper part) and on 44 EEGs at 48 h (lower part) after target temperature management. Prediction shows whether the parameter is a predictor for good or poor outcome.

120 EEGs at 24 h	Prediction	TTM24			TTM48			p-Value
		No. (%)	Specificity	Sensitivity	No. (%)	Specificity	Sensitivity	Spec/sens
Westhall model								
Highly malignant	Poor	16 (28)	87 (73–96)	61 (36–83)	11 (17)	93 (82–99)	47 (23–72)	0.83/0.65
Malignant	Poor	29 (51)	44 (28–60)	39 (17–64)	31 (49)	52 (37–67)	53 (28–77)	0.64/0.61
Benign	Good	12 (21)	100 (81–100)	31 (17–48)	21 (33)	100 (80–100)	46 (31–61)	1.00/0.35
Hofmeijer model								
Unfavorable	Poor	2 (4)	100 (91–100)	11 (1–35)	1 (2)	100 (92–100)	6 (0–29)	1.00/1.00
Intermediate	Poor	32 (56)	56 (40–72)	83 (59–96)	36 (57)	57 (41–71)	94 (71–100)	1.00/0.81
Favorable	Good	23 (40)	94 (73–100)	56 (40–72)	26 (41)	100 (80–100)	57 (41–71)	0.91/1.00
44 EEGs at 48 h								
Westhall model								
Highly malignant	Poor	3 (27)	100 (29–100)	38 (9–76)	3 (9)	95 (76–100)	17 (2–48)	1.00/0.62
Malignant	Poor	6 (55)	67 (9–99)	63 (24–91)	19 (58)	48 (26–70)	67 (35–90)	1.00/0.93
Benign	Good	2 (18)	100 (63–100)	67 (9–99)	11 (33)	83 (52–98)	43 (22–66)	0.78/0.64
Hofmeijer model								
Unfavorable	Poor	2 (18)	100 (29–100)	25 (3–65)	0 (0)	100 (84–100)	0 (0–26)	NA/NA
Intermediate	Poor	7 (64)	67 (9–99)	75 (35–97)	16 (48)	62 (38–82)	67 (35–90)	1.00/0.87
Favorable	Good	2 (18)	100 (63–100)	67 (9–99)	17 (52)	67 (35–90)	62 (38–82)	0.55/1.00

TTM24 = targeted temperature management for 24 h group. TTM48 = targeted temperature management for 48 h group. P-values from Fischers exact or Chi square test indicate differences between TTM24 and TTM48 groups. Specificities and sensitivities are presented with 95% confidence intervals in parentheses. EEG at 24 h: EEG recorded 12–24 h after reaching target temperature. EEG at 48 h: EEG recorded 36–48 h after reaching target temperature. NA = not applicable, because of no patients in one of the groups.

higher sensitivity in Hofmeijers "favorable" category compared to Westhalls "benign" category (p = 0.06, data not shown).

Westhall: There were few patients in the categories and no significant differences in specificities and sensitivities in the TTM24 group compared with the TTM48 group (Table 2).

Hofmeijer: Only two patients from the TTM24 group were in the "unfavorable" category, both with poor outcome. Nineteen patients, two in the TTM24 group and 17 in the TTM48 group had a "favorable" EEG, 16 of whom had a good outcome (Table 2).

Absence of SSEP at 48 h had a specificity of 100% for prediction of poor outcome with a sensitivity of 21%.

Prognostication at 24 or 48 h

In 44 patients, an EEG was recorded at both 24 h and 48 h. We compared prognostic ability at the two time-points (Table 4).

Westhall: In favor of prognostication at 24 h, five patients (11%) with a good outcome changed category to a wrong category

Table 3 – Prediction of poor and good outcome by two EEG classifications, somatosensory evoked potentials (SSEP), and EEG reactivity on 120 patients 24 h after reaching target temperature and on 44 patients 48 h after reaching target temperature.

	No. (%)	FPR	Specificity	Sensitivity	PPV	NPV
Prediction of poor outcome						
EEG features						
Westhall model						
EEG at 24 h (n = 120)						
Highly malignant	27 (23)	9 (4–18)	91 (82–96)	54 (37–71)	70 (50–86)	83 (74–90)
Malignant	60 (50)	52 (41–63)	48 (37–59)	46 (29–63)	27 (16–40)	68 (55–80)
EEG at 48 h (n = 44)						
Highly malignant	6 (14)	4 (0–21)	96 (79–100)	25 (9–49)	83 (36–100)	61 (43–76)
Malignant	25 (57)	50 (29–71)	50 (29–71)	65 (41–85)	52 (31–72)	63 (38–84)
Hofmeijer model						
EEG - 24 h (n = 120)						
Unfavorable	3 (3)	0 (0–4)	100 (96–100)	9 (2–23)	100 (29–100)	73 (64–80)
Intermediate	68 (57)	44 (33–55)	56 (45–67)	89 (73–97)	46 (33–58)	92 (81–98)
EEG at 48 h (n = 44)						
Unfavorable	2 (5)	0 (0–14)	100 (86–100)	10 (1–32)	100 (16–100)	57 (41–72)
Intermediate	23 (52)	38 (19–59)	63 (41–81)	70 (46–88)	61 (39–80)	71 (48–89)
SSEP						
Bilaterally absent at 24 h (n = 86)	6 (7)	0 (0–6)	100 (94–100)	23 (9–44)	100 (54–100)	75 (64–84)
Bilaterally absent at 48 h (n = 26)	3 (12)	0 (0–26)	100 (74–100)	21 (5–51)	100 (29–100)	52 (31–73)
EEG reactivity						
Absent reactivity at 24 h (n = 120)	71 (59)	45 (34–56)	55 (44–66)	94 (81–99)	46 (35–59)	96 (86–100)
Absent reactivity at 48 h (n = 44)	26 (62)	48 (27–69)	52 (31–73)	79 (54–94)	58 (37–77)	75 (48–93)
Prediction of good outcome						
EEG features						
Westhall model						
EEG at 24 h (n = 120)						
Benign	33 (28)	0 (0–10)	100 (90–100)	39 (28–50)	100 (89–100)	40 (30–51)
EEG at 48 h (n = 44)						
Benign	13 (30)	10 (1–32)	90 (68–99)	46 (26–67)	85 (55–98)	58 (39–75)
Hofmeijer model						
EEG - 24 h (n = 120)						
Favorable	49 (41)	3 (0–15)	97 (85–100)	56 (45–67)	98 (89–100)	48 (36–60)
EEG at 48 h (n = 44)						
Favorable	19 (43)	20 (6–44)	80 (56–94)	63 (41–81)	79 (54–94)	64 (43–82)
EEG reactivity						
Present reactivity at 24 h (n = 120)	49 (41)	77 (56–91)	94 (81–99)	55 (44–66)	96 (86–100)	46 (35–59)
Present reactivity at 48 h (n = 44)	18 (41)	52 (31–73)	48 (27–69)	21 (6–46)	25 (7–52)	42 (23–63)

FPR = False Positive Rate (ratio between number of false positives and number of patients with a good outcome). Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) in percentage with 95% confidence interval in parentheses.

(Fig. 2). Oppositly, two patients (5%) in a category at 24 h that did not correctly predict their outcome shifted to correct categories at 48 h.

A "highly malignant" pattern was present in six of the 44 patients (14%) at 48 h after reaching TT with no difference in prevalence between TTM groups (p = .18). One of these patients with a burst-suppression pattern had a good outcome, and the remaining five patients all had a poor outcome.

Hofmeijer: From 24 h to 48 h, three patients (7%) changed from a correctly predicting category to a wrong category. Seven patients (16%) changed in the opposite direction from a category that did not correctly predict outcome to a correctly predicting category at 48 h. No patients with an "unfavorable" pattern at any time-point had a good outcome.

We found no significant differences in specificities or sensitivities at 24 h versus 48 h in either of the two models. However, we found a significantly higher specificity of present EEG reactivity at 24 h compared with 48 h after reaching TT ($p < 0.001$) and in the TTM48 group at 48 h we found a tendency towards more continuous and reactive EEGs (p = .10).

Discussion

We found no significant differences between TTM groups in specificity and sensitivity as assessed on a dichotomized CPC-scale after six months, however, numbers were small in each group at 48 h and our results should be validated in larger trials. We found no significant differences between prognostication at 24 h compared to 48 h measured in specificity and sensitivity of EEG categories, but using EEG reactivity, prognostication was best at 24 h compared to 48 h. Both classification models performed best in good outcome prediction.

Table 4 – Prediction of poor and good outcome by two EEG classifications at 24 h and 48 h based on 44 EEGs recorded 12-24 h (24 h) and 36-48 h (48 h) after reaching target temperature. P-values from Mc Nemars test comparing specificity and sensitivity at 24 h and 48 h.

	No. (%)	Specificity	Sensitivity	No. (%)	Specificity	Sensitivity	Spec/sens
Predictors of poor outcome							
44 EEGs at 24 h and 48 h	24 h			48 h			p-Value
Westhall model							
Highly malignant	11 (25)	92 (73–99)	45 (23–68)	6 (14)	96 (79–100)	25 (9–49)	1.00/0.13
Malignant	23 (52)	50 (29–71)	55 (32–77)	25 (57)	50 (29–71)	65 (41–85)	1.00/0.69
Hofmeijer model							
Unfavorable	1 (2)	100 (86–100)	5 (0–25)	2 (5)	100 (86–100)	10 (1–32)	1.00/1.00
Intermediate	30 (68)	54 (33–74)	95 (75–100)	23 (52)	63 (41–81)	70 (46–88)	0.73/0.13
Predictors of good outcome							
	24 h			48 h			p-Value
Westhall model							
Benign	10 (23)	100 (83–100)	42 (22–63)	13 (30)	90 (68–99)	46 (26–67)	0.50/1.00
Hofmeijer model							
Favorable	13 (30)	100 (83–100)	54 (33–74)	19 (43)	80 (56–94)	63 (41–81)	0.13/0.45

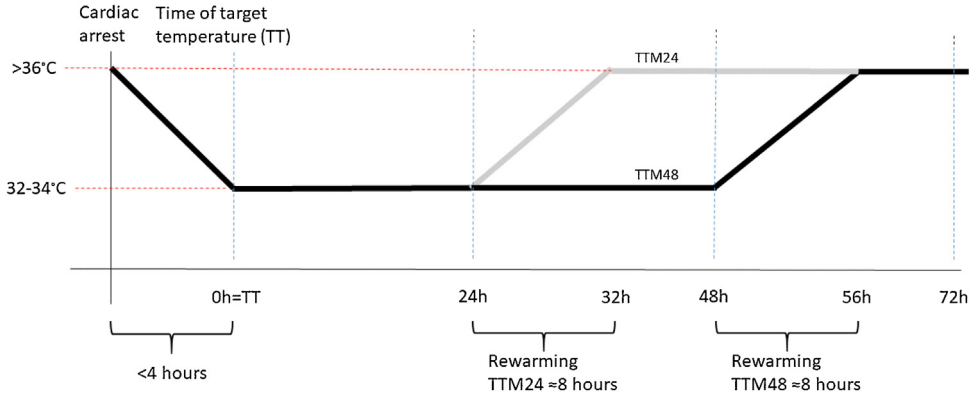

Fig. 2 – Time frame from cardiac arrest until after rewarming of both target temperature management (TTM) groups. TTM24 = group treated with target temperature management for 24 h. TTM48 = group treated with target temperature management for 48 h. EEG = electroencephalography performed at 12-24 h (24 h EEG) and at 36-48 h (48 h EEG).

Prognostication at 24 h or 48 h

We found no statistically significant differences between prognostication using the two models by Westhall and Hofmeijer at 24 h versus 48 h, but in the EEG categories predicting good outcome we found a non-significant difference in favor of prognostication at 24 h. Good outcome prediction using EEG reactivity was significantly in favor of 24 h prediction, and thus we align with several studies, indicating that prognostication is as good or better at ≤24 h compared to later.[13–15]

Differences between the two models in prediction of poor outcome

The Hofmeijer classification model was intended as an early (12–24 h) prediction model. In contrast, Westhall et al. presented a classification model based on routine EEGs recorded at a median of 77 h after cardiac arrest, intended for prognostication in normothermic patients at a minimum of 36 h after cardiac arrest. When applied to our patients, the Westhall model lacked specificity due to the burst-suppression patterns that were classified as "highly malignant". This particular misclassification was somewhat anticipated since the model was based on EEGs recorded beyond 48 h after cardiac arrest, and not as early as 24 h as in our study. In two recent studies,[16,17] specificity reached 98% when the model was applied on EEGs recorded with a median of 76 h[16] and 39 h post cardiac arrest.[17]

Likewise, the eight false positives of the Westhall model in our cohort at 24 h all presented with a burst-suppression pattern, which is known to be potentially transient when seen early[14,18] and not recommended to be used for prognostication during the first 24–36 h after cardiac arrest.[19]

The Hofmeijer model had high specificity for prediction of poor outcome but very low sensitivity. The low sensitivity could be due to the fact that suppression with periodic discharge and burst-suppressions were not included in the classification of poor outcome patterns as in the Westhall model.

As in the Hofmeijer study, we had no false positive predictions in the "unfavorable" category but the prevalence of this category was markedly different with 41/113 in the Hofmeijer study as opposed to 3/

120 in our study (Table 3) even though time of EEG recordings were similar. This difference could be related to differences in treatment as reflected by the high prevalence of good outcome in our study.

Prevalence of "highly malignant" patterns (27/120 at 24 h) were closer when comparing our study with the Westhall study (38/103 at > 36 h) despite differences in time of EEG recordings. The Westhall model predicted more patients with poor outcome in our study at 24 h compared to the Hofmeijer model, but with a false positive rate of 9%.

EEG reactivity

Absence of reactivity during hypothermia was strongly related to poor outcome with no false positives[14] in a study by Rossetti et al., and only one false positive prediction in 47 patients with absence of reactivity in a study by Oddo et al.[13] This could not be confirmed by our study, which is in accordance with suggestions of current guidelines on not using absence of reactivity in isolation for prediction of poor outcome.[19]

Differences between the two models in prediction of good outcome

At 24 h, the Hofmeijer model predicted more patients with good outcome than the Westhall model (49 versus 33 patients respectively) with only one false positive prediction in the Hofmeijer model. The falsely predicted patient died from cardiac failure. In a recent study from Rossetti et al.[20], presence of EEG reactivity performed well as a predictor of good outcome and including this in predictive models may further improve prediction of good outcome. We found high predictive performance for good outcome in both models.

Specific patterns in outcome prediction

Burst-suppression was of special interest in our cohort since all eight false positives at 24 h in the Westhall "highly malignant" group had a burst-suppression pattern and we even found one patient that still had burst-suppression at 48 h. This emphasizes the advice of current guidelines on not using burst-suppression for prognostication during the first 24–36 h.[19] Surviving a burst suppression pattern at 48 h is to our knowledge only described once in a recent study by Backman et al.[16] and might be due to ongoing sedation or a possible protective effect of prolonged TTM. In the Hofmeijer model they included a burst-suppression pattern with identical bursts in their "unfavorable" classification. This is, however, a rare pattern seen mostly transiently in EEGs recorded before 36 h, as described in a study by Hofmeijer et al. where they report an incidence of 20% in 101 cardiac arrest patients.[21] We found no patients presenting with this EEG pattern in our cohort. In the TTM48 group at 48 h we found an interesting trend towards more continuous and reactive EEGs in the TTM48 group ($p = .10$) contrary to what would be expected since the TTM48 group was still under TTM and sedated. This could be a result of the fact that the TTM24 patients at 48 h were more prone to poor prognosis and therefore were less likely to present with patterns indicating good prognosis. The ability to predict poor outcome would be expected to increase over time due to this effect. However, we could not show this effect in our cohort.

Limitations

This study is limited by missing EEGs at 48 h, resulting in few patients in each group, introducing a risk of selection bias due to the theoretical skewness between TTM groups at 48 h. A potential problem in unblinded studies investigating prognostic accuracy is the self-fulfilling prophecy.[22,23] In our study, clinicians were blinded to the results of EEG, except in cases of seizure activity, and to the results of SSEP recordings performed for research purposes, but standard EEG and SSEP on clinical indication were still recorded independent from our examinations.

Conclusion

Our results suggest no differences in prognostication between TTM groups using two models proposed by Westhall and Hofmeijer. We found no significant differences at 24 h compared to 48 h measured in specificity and sensitivity of EEG categories, but using EEG reactivity, prognostication was significantly better at 24 h compared to 48 h. Both classification models performed very well in good outcome prediction. Models for prediction of poor outcome within 48 h should not include non-identical burst-suppression as a predictor.

Conflicts of interest

Christophe H. V. Duez received funding from the following private foundations: The Viggo and Helene Bruun foundation, the Lily Benthine Lunds foundation of 1st of june 1978, the Director Jacob Madsen & wife Olga Madsen foundation and the Grocer A. V. Lykfeldt and wife foundation. Foundations had no influence on study design, data collection, analysis or data interpretation.

Acknowledgements

We wish to thank the staffs at the intensive care units of Stavanger University Hospital and Aarhus University hospital.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.resuscitation.2018.10.035.

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