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Multimodal outcome prognostication after Cardiac Arrest and Targeted Temperature Management: analysis of 36 °C

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Abstract

Introduction: Targeted Temperature Management (TTM) represents the standard of care in comatose survivors after cardiac arrest (CA), and may be applied targeting 33° or 36°C. While multimodal prognostication has been extensively tested for 33°C, scarce information exists for 36°C.

Methods: In this cohort study, consecutive comatose adults after CA treated with TTM at 36°C between July 2014 and October 2016 were included. A combination of neurological examination, electrophysiological features, and serum Neuron Specific Enolase (NSE) was evaluated for outcome prediction at three months (mortality; good outcome defined as Cerebral Performance Categories (CPC) score of 1-2, poor outcome defined as CPC 3-5).

Results: We analysed 61 patients. Presence of 2 or more predictors out of: unreactive EEG background, epileptiform EEG, absent pupillary and/or corneal reflex, early myoclonus, bilaterally absent cortical SSEP, and serum NSE >75 μg/l had a high specificity for predicting mortality (PPV = 1.00, 95%CI 0.87-1.00) and poor outcome (PPV = 1.00, 95%CI 0.80-1.00). Reactive EEG background was highly sensitive for predicting good outcome (0.95, 95%CI 0.74-0.99).

Conclusion: Prediction of outcome after CA after TTM targeting 36°C seems valid in adults using the same features tested at 33°C. A reactive EEG under TTM appears highly sensitive for good outcome.

Introduction

Cardiac arrest (CA) has an annual incidence of 50-110 /100000 (1), with an approximately 10% successful resuscitation rate (2) and a remarkable mortality decrease of hospitalized patients in the last few years (3). Targeted Temperature Management (TTM), with Therapeutic Hypothermia (TH) to 33°C (4) or more recently targeting 36°C (5), has likely contributed to this trend (6). In this setting, clinicians are expected to quickly and accurately provide predictions of survivors' outcome.

Several predictors have been standardized following TH. Specifically, bilateral absence of brainstem reflexes, absence of motor response to pain and treatment-resistant myoclonus (7-10) unreactive or discontinuous EEG background activity (10-12) bilateral absence of N20 Somatosensory Evoked Potentials (SSEP) (7) and high serum Neuron Specific Enolase (NSE) (13) are related to poor neurological recovery. However, during TH, sedative medications and possibly the temperature itself may delay prognostication decision up to several days, especially regarding motor signs (14).

After showing no difference in mortality between survivors treated with TH and survivors treated with 36°C (5,15), guidelines for care after CA are changing and foresee the use of TTM, either targeting 33°C or 36°C, depending on patients' profiles (16). The above-mentioned predictors (especially clinical examination, possibly also neurophysiological tests and NSE) are potentially influenced by the temperature degree and subsequent myorelaxant medication; therefore they have been thoroughly tested in patients treated with TTM at 36°C and showed, individually, their validity in this condition (17-19).

Independently of the TTM target, a multimodal approach of the above-mentioned tests is strongly advocated in order to provide an early and accurate outcome prediction. Our group has focused on this strategy since the TH era and already validated the use of a protocol combining clinical examination and neurophysiological features for taking decisions upon continuation of intensive

treatment (10,20). Relatively little is known, however, regarding such an approach in patients undergoing 36°C. The aim of our study was to assess accuracy of this multimodal prognostic panel in patients treated with 36°C.

Methods

Study Subjects and TTM

In this cohort study, we prospectively collected consecutive patients older than 18 years successfully resuscitated after CA (in-hospital : out-of-hospital CA ratio was 1:10), who were managed with TTM in the medical-surgical intensive care unit at the University Hospital of Lausanne, between July 2014 and October 2016. Patients that died within 24 hours after CA were excluded. Our institutional ethic committee fully approved this study. Patients were managed with TH until July 2014, then with either TH or 36°C (5), depending on the patient context until May 2016, and thereafter exclusively with 36°C. According to our protocol (in analogy to 33°C) (10), 36°C target-temperature was applied for 24 hours using ice packs and intravenous ice-cold fluids together with a surface cooling device (Arctic Sun System, Medivance, Louisville), with passive rewarming after 24 hours. Midazolam (0.1 mg/kg/h) and fentanyl (1.5 μg/kg/h) were given for analgesia-sedation, and vecuronium for shivering.

Neurological and Outcome Assessment

Neurological examination, including principal brainstem reflexes (pupillary, oculocephalic, corneal) and motor reactivity to pain stimulation, was assessed by a certified neurologist after interruption of TTM and weaning of pharmacological sedation (at least twice between 36 and 72 hours after CA, or more often if needed). EEG recordings were assessed during (at least 6 hours after CA, under TTM and sedation), and early after TTM, at the time of clinical examination. EEG background reactivity interpretation was performed by two experienced electroencephalographers (JN, AOR). Bilateral median nerve Somatosensory Evoked Potentials (SSEP) were recorded at least 24 hours after CA. Serum Neuron Specific Enolase (NSE) was measured at 24 and 48 hours after CA and analysed with an automated immunofluorescent assay (Thermo Scientific Brahms NSE Kryptor Immunoassay,

Hennigsdorf, Germany). Withdrawal of care was decided using a multidisciplinary approach, if two or more of the following criteria were present after TTM and after sedation was withdrawn (10): 1. Unreactive EEG backround 2. Treatment-resistant myoclonus, 3. Bilateral absence of N20 in SSEP, and 4. Incomplete return of brainstem reflexes.

Outcome at 3 months was assessed through a semi-structured phone interview using Cerebral Performance Categories (CPC) (21,22): CPC 1 indicates full recovery; CPC 2 moderate disability; CPC 3 severe disability; CPC 4 coma or persistent vegetative state, and CPC 5 death. Poor neurological outcome was defined as CPC 3 to 5.

Data Collection and Variable Definitions

CA etiology was dichotomized as cardiac and non-cardiac, and initial arrest rhythm as ventricular fibrillation (VF) and non-VF (asystole and pulseless electrical activity). Time to return of spontaneous circulation (ROSC) was based on paramedics' reports. The best clinical features of the clinical assessments performed within the first 72 hours were used for analysis. Early myoclonus was retained if occurred in the first 24 hours after weaning of sedation, or if seen earlier. Treatment-resistant myoclonus was defined as persistent despite treatment with at least two antiepileptic drugs (23). EEG reactivity was assessed with bilateral nipple pinching and was defined as a reproducible change in amplitude or frequency, excluding stimulus-induced rhythmic, periodic or irritative discharges (SIRPIDs) and muscle artifacts (24), add Fantaneanu Clin Neurophysiol 2016; epileptiform activity as any repetitive periodic or rhythmic spikes, or sharp waves, or spike-waves (25). The N20 (cortical) responses on SSEP were categorized as present or bilaterally absent, regardless of the amplitude. The NSE peak level was considered for the purpose of this study. All variables were collected prospectively according to the Utstein style (26).

Statistical Analysis

The cohort was analyzed using Fischer, Student *t* and Mann-Whitney *U* tests as needed. Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) were assessed for poor outcome (CPC 3-5), using an exact binomial 95% confidence interval (CI), for unreactive first (during TTM) EEG background, epileptiform first EEG, absence of pupillary and/or corneal reflex, early myoclonus, bilaterally absent N20 on SSEP, NSE level above 75 μg/l (20). To

evaluate the performance of all above-mentioned variables, both for mortality and poor neurological outcome, unweighted accuracies and areas under receiver operating characteristic (ROC) curves were calculated. Finally, we explored the value of a reactive first EEG background for good (CPC 1-2) outcome. Calculations were performed with Stata software, version 12 (College Station, TX). Significance was set at $p < 0.05$.

Results

From July 2014 to October 2016, 137 patients have been successfully resuscitated after CA and admitted to our intensive care unit; 61 of them were treated with TTM at 36°C and are the object of this study, the other 76 were treated at 33°C. **Table 1** shows their demographics and clinical characteristics.

Table 2 illustrates predictors of poor outcome: all had high PPV but early myoclonus, epileptiform EEG, bilaterally absent N20, and NSE level above 75 µg/l correlated with no false positivity. On the other hand, a reactive EEG background activity represented a sensitive predictor of good outcome for both groups as shown in **Table 3**.

Testing the multimodal approach, the presence of two or more of the above mentioned parameters had a high specificity for predicting both poor outcome and mortality (**Table 4**). This was confirmed by the ROC curves (**Tables 4a,b, figure 1**).

Discussion

These findings suggest that early multimodal prediction of mortality and poor functional outcome in survivors after CA is reliable in patients after TTM at 36°C with parameters routinely used at 33°C. Furthermore, a reactive EEG under TTM at 36°C and sedation seems highly sensitive for predicting good outcome in both conditions.

Medical decisions in this clinical setting should never be based on isolated tests and the need of a multimodal approach is widely recommended (27-29). Recent studies assessed outcome predictors comparing 33°C vs 36°C, mostly generated by the TTM trial (5,30) (for a detailed discussion, see below); they however focused on isolated tests and not on multimodality. Our findings show high specificity of a first unreactive EEG background for predicting poor outcome at 36°C. Besides background amplitude (31,32), reactivity has been repeatedly described (10,12,33-35); however, as opposed to this study, those description rely on patients treated with 33°C and the first EEG recorded during TTM is generally not included as a predictor in current recommendations (28,36). We acknowledge that lack of standardized stimulations (24) remains a relevant limitation. On the other hand, early epileptiform EEG features during TTM accurately predicted poor outcome, with no false positives, which is already known after TTM at 33°C (10,11), but also during hypothermia and sedative medications with antiepileptic effect (20,27,37). The role of EEG background reactivity for good outcome has recently been shown after 33°C (10,20,34) and is confirmed by the present study also in the 36°C group. Finally, bilateral absence of the N20 response in SSEP is highly correlated with poor outcome after CA and TTM (7,20); this study's findings in line with these previous results in both temperature groups.

Clinical examination represents a paramount test in this setting. Bilateral absence of pupillary or corneal reflexes as well as early myoclonus are already recognized outcome predictors after 33°C (8,10,30), and are confirmed by this study for 36°C. The absence of a motor response to pain represented an important test before TTM era[8] but its early evaluation in TTM is altered from myorelaxant or sedative medication (10,38). Early myoclonus is consistently associated with poor outcome (8,9), but a careful assessment is necessary in order to avoid wrong therapeutic decisions in patients with treatable postanoxic Lance-Adams syndrome. Furthermore, some isolated cases of good prognosis after treatment have been described (23,39), underscoring the importance of multimodality.

High serum NSE levels reflect the degree of brain damage after CA; prior to the TH era, a level above 33 μg/l at 48 hours after CA was considered robustly predictive of poor outcome (40). During TTM, this cut-off value has been questioned; a high

predictive value of poor outcome has been reported, independently of target temperature and with values consistently higher than 33 μg/l (19). Given the difficulty in identifying clear cut-offs, independent of settings, laboratories and sedations/temperatures, NSE is currently not routinely used as a core test after CA (27). Our findings confirm a cut-off of >75 μg/l for poor outcome in TTM at 36°C with no false positives, in line with our previous work (20).

The presence of two or more of the above-analysed variables accurately predicted both poor functional outcome and mortality, with very high accuracy in adult patients undergoing TTM at 36°C. The previously described multimodal approach for predicting poor outcome was based on EEG recorded after TTM and off sedation (10) (even though, subsequently, EEG during TH was find to be even more accurate (20)) and incomplete brainstem reflexes, and didn't take into account epileptiforn EEG features or NSE values. Furthermore, the previous method was tested only in patients treated at 33°C. In view of the present findings, it seems that this can be used also in controlled TTM targeting 36°C.

This study has limitations. In our registry we unfortunately lack data allowing identification of patients who had decisions of withdrawal of intensive care support, and we recognize that a self-fulfilling prophecy was potentially at play, as several predictors described here were used in practice for decisions on discontinuation of intensive care support. However, this should not apply to EEG (we routinely consider EEG after TTM, but not during TTM) and serum NSE; this should limit the self-fulfilling impact on these variables, albeit –admittedly- all results were available to clinicians. Unfortunately, this sort of problem is inherent to virtually all studies conducted in this clinical setting (10, 27). We believe that a well structured multimodal approach represents the only strategy to counteract this problem. Even if it seems highly accurate in the acute phase, this multimodal approach may not be absolutely specific in view of the relatively low number of patients and the 95% confidence intervals: rapid conclusions should be avoided, especially in doubtful cases. Moreover, this multimodal approach didn't explore which combination of tests was the most accurate, as for this a larger cohort would be necessary. Finally, the serum NSE cutoff value of 75 μg/l, was identified a priori (20).

Conflicts of interest: The authors declare that they have no conflict of interest.

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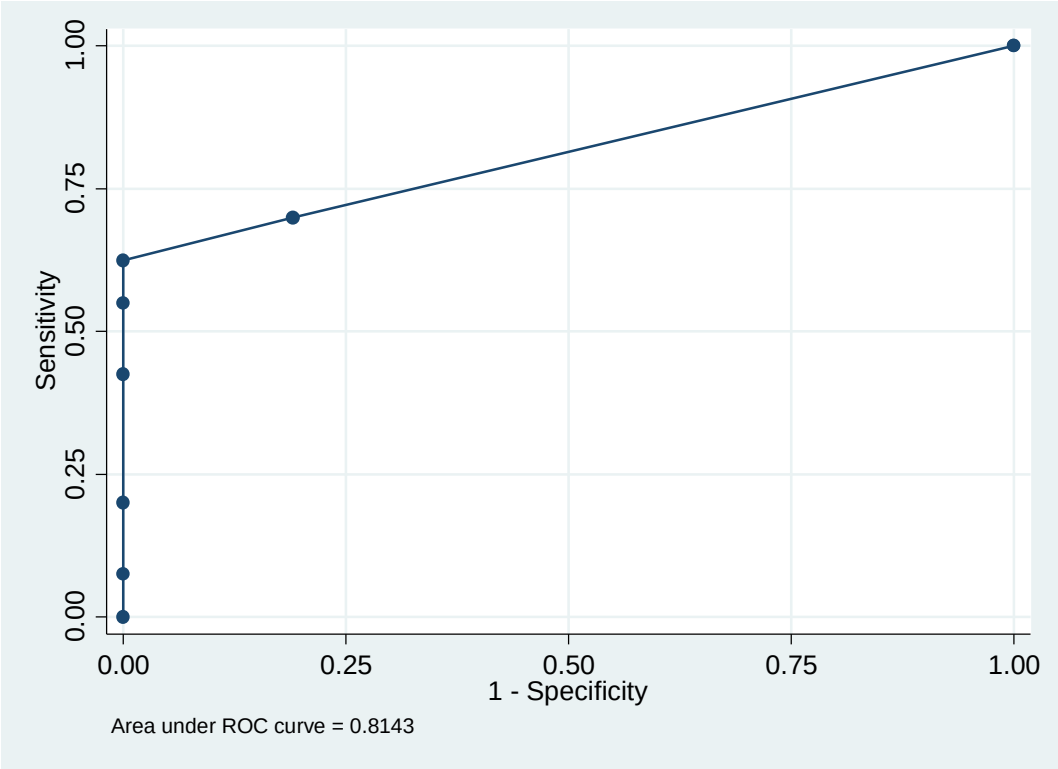

Figure 1: Prognostic value of the multimodal approach for prediction poor outcome using the receiver operator characteristic (ROC) curves (presence of 2 or more variables among unreactive first EEG background, epileptiform first EEG, absent pupillary and/or corneal reflex, early myoclonus bilaterally absent SSEP, and NSE> 75 µg/l)
EEG=Electroencephalogram, NSE =Neuron Specific Enolase, SSEP= Somatosensory Evoked Potentials.

Table 1: Clinical characteristics of the studied cohort. TTM = Targeted Temperature Management, CPC= Cerebral Performance Categories, SD= Standard Deviation, VF= ventricular Fibrillation, CA= Cardiac Arrest, ROSC= Return of Spontaneous Circulation, EEG= Electroencephalogram, SSEP= Somatosensory Evoked Potentials, NSE= Neuron Specific Enolase

Characteristic	**TTM 36°C n=61 (35%)**
Survivors, No (%)	33/61 (54%)
Outcome, No (%) CPC 1 CPC 2 CPC 3 CPC 4 CPC 5	 10 (16%) 11 (18%) 10 (16%) 0 (0%) 30 (49%)
Good outcome (CPC 1-2), No (%)	21/61 (34%)
Age, mean yr SD (range)	66±13.7 (25-87)
Female gender, No (%)	22/61 (36%)
Non-cardiac etiology, No (%)	21/61 (34%) *Missing: 1*
Non-VF CA, No (%)	35/61 (57%)
Time to ROSC, median min SD (range)	18± 25.8 (2-180)
Absent Pupillary reflex, No (%)	12/61 (20%)
Absent Corneal reflex, No (%)	19/61 (31%)
Absent Motor response, No (%)	28/61 (46%)
Early myoclonus, No (%)	13/61 (21%)
Unreactive background first EEG, No (%)	27/60 (45%) *Missing 1*
Unreactive background second EEG, No (%)	16/55 (29%) *Missing 6*
Epileptiform first EEG, No (%)	14/60 (23%) *Missing 1*
Bilaterally absent N20 on the SSEP, No (%)	20/55 (36%) *Missing 6*
NSE, median µg/l SD (range)	34±86 (12-391.1)
NSE >75 µg/l, No (%)	12/45 (27%) *Missing 16*
Time to first EEG, median hours SD (range)	22±8.2 (5.5-46)
Time to SSEP, median hours, SD (range)	24±18.7 (24-96)

Table 2: Prognostic value for poor outcome (CPC 3-5)
EEG=Electroencephalogram, NSE =Neuron Specific Enolase, SSEP= Somatosensory Evoked Potentials, PPV= Positive Predictive Value, NPV= Negative Predictive Value, CI=Confidence Interval

Characteristic	Sensitivity	Specificity	PPV	NPV
Absent Pupillary reflex	0.27 (95%CI 0.15-0.44)	0.95 (95% CI 0.74-0.99)	0.90 (95% CI 0.59-0.99)	0.40 (95%CI 0.27-0.55)
Absent Corneal reflex	0.43 (95%CI 0.27-0.59)	0.90 (95%CI 0.68-0.98)	0.89 (95%CI 0.65-0.98)	0.45 (95%CI 0.30-0.61)
Unreactive background first EEG	0.67 (95%CI 0.49-0.80)	0.95 (95%CI 0.74-0.99)	0.96 (95%CI 0.79-0.99)	0.60 (95%CI 0.42-0.76)
Epileptiform first EEG	0.36 (95%CI 0.21-0.52)	1.00 (95%CI 0.8-1)	1.00 (95%CI 0.73-1)	0.46 (95%CI 0.31-0.60)
NSE >75 μg/l	0.4 (95%CI 0.23-0.59)	1.00 (95%CI 0.74-1)	1.00 (95%CI 0.69-1)	0.45 (95%CI 0.28-0.63)
Early myoclonus	0.33 (95%CI 0.19-0.49)	1.00 (95%CI 0.8-1.0)	1.00 (95%CI 0.71-1.0)	0.43 (95%CI 0.29-0.58)
Bilaterally absent N20 on the SSEP	0.53 (95%CI 0.36-0.69)	1.00 (95%CI 0.77-1)	1.00 (95%CI 0.79-1)	0.48 (95%CI 0.31-0.65)

Table 3: Prognostic value for good outcome (CPC 1-2)
EEG=Electroencephalogram, PPV= Positive Predictive Value, NPV= Negative Predictive Value, CI=Confidence Interval

Characteristic	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Reactive first EEG background	0.95 (95%CI 0.74-0.99)	0.66 (95%CI 0.49-0.80)	0.60 (95%CI 0.42-0.76)	0.96 (95%CI 0.79-0.99)

Table 4a, b: Prognostic value of the multimodal approach for poor outcome and mortality (presence of 2 or more variables among unreactive first EEG background, epileptiform first EEG, absent pupillary and/or corneal reflex, early myoclonus bilaterally absent SSEP and NSE> 75 μg/l)
EEG=Electroencephalogram, NSE =Neuron Specific Enolase, SSEP= Somatosensory Evoked Potentials, PPV= Positive Predictive Value, NPV= Negative Predictive Value, CI=Confidence Interval, ROC= Receiver Operating Characteristic

a	**Poor outcome**
Sensitivity	0.62 (95%CI 0.45-0.76)
Specificity	1.00 (95%CI 0.80-1.00)
PPV	1.00 (95%CI 0.83-1.00)
NPV	0.58 (95%CI 0.40-0.74)
Area under the ROC	0.81 (95% CI: 0.70-0.91)
b	**Mortality**
Sensitivity	0.82 (95%CI 0.62-0.93)
Specificity	1.00 (95%CI 0.87-1.00)
PPV	1.00 (95%CI 0.82-1.00)
NPV	0.86 (95%CI 0.71-0.95)
Area under the ROC	0.91 (95% CI: 0.81-0.97)