Prognostication of Coma After Cardiac Arrest and Therapeutic Hypothermia

M. Oddo

Introduction

Following the introduction of therapeutic hypothermia and the implementation of standardized post-resuscitation care, the number of patients who survive from coma after cardiac arrest has significantly increased [1]. Previous to use of therapeutic hypothermia, clinical neurological examination at 72 hours was considered the gold standard for outcome prognostication of coma after cardiac arrest [2]. However, therapeutic hypothermia and the drugs used to induce therapeutic cooling alter drug elimination and may significantly modify neurological (mainly motor) response [3, 4], thereby rendering clinical examination less reliable and potentially insufficient, when used alone, to adequately predict the prognosis of coma after cardiac arrest. Emerging evidence from independent centers demonstrates that the addition to neurological examination of other prognostic tools – mainly electroencephalography (EEG), somato-sensory evoked potentials (SSEP) and serum neuron-specific enolase (NSE) – significantly improves prognostication of coma after cardiac arrest and therapeutic hypothermia. The implementation of such a multimodal prognostic approach into critical care practice should improve the care of comatose cardiac arrest patients.

M. Oddo (✉)
Department of Critical Care Medicine, CHUV-Lausanne University Hospital and Faculty of Biology and Medicine, University of Lausanne, Rue du Bugnon 46, BH 08.623, CH-1011 Lausanne, Switzerland
e-mail: mauro.oddo@chuv.ch

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Neurological Examination to Assess Prognosis After Cardiac Arrest and Therapeutic Hypothermia

Clinical examination is an essential step to assess prognosis; however, recent clinical studies have shown that neurological tests may have reduced prognostic accuracy in comatose cardiac arrest patients treated with induced hypothermia.

Motor Response

Bouwes et al., in a recent study including 391 adult comatose patients after cardiac arrest treated with therapeutic hypothermia, found that motor response gave a false outcome prediction in up to 10–15 % of patients (false positive rate of 10 % for poor prognosis, with a 95 % confidence interval [CI] of 6–16) [5]. This study confirmed previous findings from other groups who found that motor response at 72 hours gave a false positive rate of 12 % [4] and up to 24 % [6] for poor prognosis. Importantly, recovery of full motor reaction may take up to 6 days after cardiac arrest and therapeutic hypothermia [3] and sedatives given during therapeutic hypothermia may also be a potential confounder [4].

Brainstem Reflexes

Although of higher predictive value than motor response, the absence of pupillary/corneal reflexes is not uniformly associated with a poor prognosis: some patients may still awake and recover, with a false positive rate of 4–6 % for poor prognosis, according to recent studies [4–7].

EEG to Improve Prognostication After Cardiac Arrest and Therapeutic Hypothermia

Analysis of Dynamic EEG Changes

Previous to the introduction of therapeutic hypothermia, the value of EEG to help with the prognostication of coma after cardiac arrest was already well known [7, 8]. In particular, the analysis of dynamic EEG changes and the dichotomization between a 'reactive' (i. e., a change in the EEG trace upon a painful stimulation) versus a 'non-reactive' EEG background was useful to discriminate between good versus poor prognosis [9].

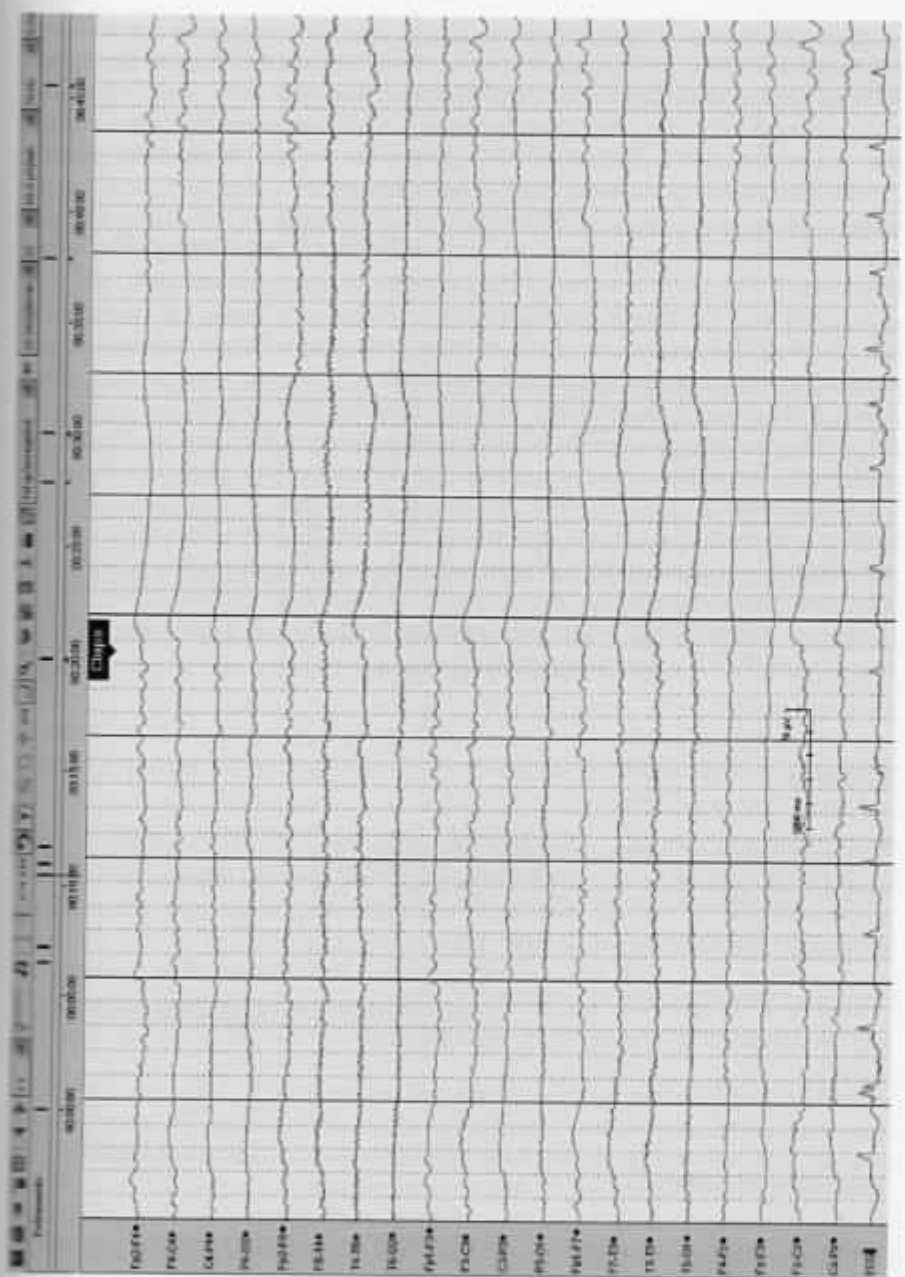

Fig. 1 EEG reactivity. The figure shows the EEG recorded on one illustrative patient during therapeutic hypothermia, 18 hours after cardiac arrest. Illustrated is an example of EEG reactivity: Upon stimulation (claps), the EEG background changes, i. e., increased frequency/reduced amplitude. The patient regained consciousness and had a good recovery

Emerging clinical evidence from several single center prospective studies suggests that EEG may indeed improve coma prognostication after cardiac arrest in patients treated with therapeutic hypothermia. Rundgren et al., in a preliminary study using a simplified amplitude-integrated EEG approach, first demonstrated that the presence of a continuous EEG pattern (as opposed to an EEG showing flat periods and/or spontaneous burst-suppression patterns) during the early hypothermic phase was associated with regain of consciousness [10]. Using the same approach, the same group more recently confirmed these findings in a larger cohort [11]. The additive value of EEG patterns to prognosticate coma after cardiac arrest and therapeutic hypothermia was further confirmed by Fugate et al., who showed that 'malignant' EEG patterns consisting of burst-suppression/generalized suppression were associated with death [7]. Finally, when looking at dynamic EEG changes, the presence of a non-reactive EEG background upon painful stimulation was also strongly associated with poor recovery [6, 7]. On the other hand, a reactive EEG background (Fig. 1) is a positive sign, which is often associated with a good recovery: our group found that all survivors had EEG background reactivity, and the majority of them (74%) had a favorable outcome at 3 months [12]. Adding EEG to standard neurological examination significantly improved outcome prediction as early as 12–24 hours from cardiac arrest – during therapeutic hypothermia – and increased the prediction of good outcome compared to SSEP [12]. Other groups had similar results [13].

Seizures

Post-anoxic seizures/status epilepticus (including myoclonus status epilepticus) are generally considered as malignant EEG patterns and are very often associated with a poor outcome [7, 14–16], particularly when occurring in the early phase during therapeutic hypothermia and sedation [12]. A subset of patients however who have 'late' seizures (i.e., after the rewarming phase) and display other 'good' signs (including EEG reactivity and presence of brainstem reflexes) may survive with a good neurological recovery [17]: these patients warrant aggressive anti-epileptic therapy.

The Role of SSEP

SSEP are usually performed to confirm a bad prognosis of coma after cardiac arrest and therapeutic hypothermia. The predictive value of SSEP for poor prognosis has indeed been confirmed in this setting by several recent studies [5–7]. Except in very rare cases [18], bilateral absence of the N20 component is invariably associated with irreversible coma and poor prognosis [19]. The main limitation of SSEP is when predicting the potential for good recovery in patients who have an N20 component but show coma or impairment of consciousness. For patients in such

a 'gray zone' of uncertain prognosis, a multimodal approach (including neurological examination, EEG and NSE) is strongly recommended: In this context, EEG reactivity significantly improves prognostic accuracy, because those patients with a reactive EEG background have a high chance of recovery [6, 12, 17].

Serum Neuron-Specific Enolase

Serum NSE is a marker of the severity of global brain ischemia and at present appears to be the biomarker with the highest prognostic value after cardiac arrest and therapeutic hypothermia [20–22]. Before the therapeutic hypothermia era, serum NSE levels above 33 µg/l 24–72 hours after cardiac arrest were strongly, although not invariably, associated with poor prognosis [2, 5, 23]. Tiainen et al. however showed in a randomized study of patients treated with therapeutic hypothermia versus normothermia that hypothermia may significantly reduce serum NSE levels; the decreasing levels of serum NSE suggest a selective attenuation of delayed neuronal death by therapeutic hypothermia [24]. From a clinical standpoint, this study indicates that applying one single cut-off level may potentially be misleading. This suggestion has indeed been repeatedly shown by all recent studies in which the predictive value of NSE was tested and compared to that of other prognostic tools [25]. Much higher cut-off serum NSE values than 33 µg/l were necessary to reach an false positive rate of 0 % [20, 22, 26], with values as high as 78.9 µg/l needed to predict a poor outcome with a specificity of 100 % [26]. In a cohort of 61 consecutive comatose cardiac arrest patients treated with therapeutic hypothermia, we found 5 subjects who survived (of whom 3 had a full recovery) despite peak serum NSE > 33 µg/l at 48–72 hours [22]. In summary, as for all previous prognostic tools, serum NSE should be integrated into a multimodal prognostic algorithm.

Multimodal Prognostic Algorithm

The implementation of therapeutic hypothermia and of standardized post-resuscitation care has increased the number of patients who survive from acute coma after cardiac arrest and have the potential for good long-term recovery. Among early survivors, some still undergo early death in the intensive care unit (ICU) from post-cardiac arrest syndrome or refractory global brain dysfunction (absent brainstem reflexes, early myoclonus, non-reactive EEG, absent bilateral N20, highly elevated serum NSE levels) and irreversible coma. An increasing number of patients survive the early ICU phase after therapeutic hypothermia, and may eventually awaken and recover. In these patients, neurological examination (particularly motor signs) may not be enough to adequately predict prognosis: Additional prognostic tools – particularly EEG, SSEP and NSE – are of great value to improve early outcome prediction and avoid misleading prognostication (Fig. 2).

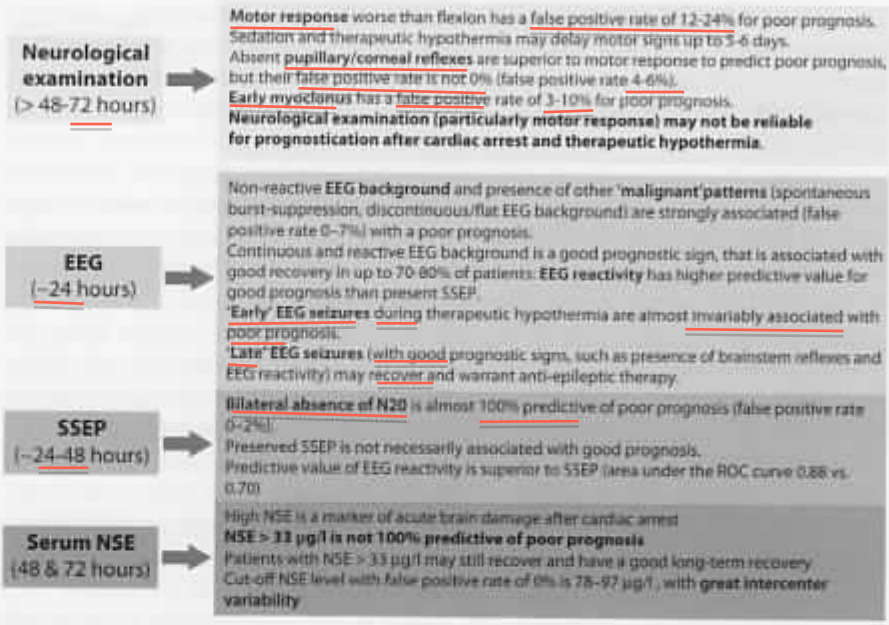

Fig. 2 Multimodal prognostication of coma after cardiac arrest and therapeutic hypothermia. The figure summarizes the timing after cardiac arrest of all available tools to predict recovery from coma. The prognostic performance is expressed as the false-positive rate for poor prognosis. EEG: electroencephalography; SSEP: somato-sensory evoked potentials; ROC: receiver operating characteristic; NSE: neuron-specific enolase

Perspectives and Areas for Future Clinical Investigation

Blood Biomarkers of Acute Cerebral Damage after Cardiac Arrest

Astrocytic soluble 100B protein (S-100B) levels have also been investigated for prognosis after cardiac arrest and studies have shown an association between elevated levels of S-100B in the blood within 24 hours from cardiac arrest and a poor prognosis [25, 27]. S-100B may represent an alternative biomarker to NSE. Preliminary studies have examined the value of other blood biomarkers, including glial fibrillary acidic protein [28], neurofilament H [29] and procalcitonin [28].

Neuroimaging

Diffusion magnetic resonance imaging (MRI) with the use of apparent diffusion coefficient (ADC) maps has been recently used to quantify brain damage after cardiac arrest and therapeutic hypothermia [30–33]. Spatial and temporal differ-

ences in ADC may provide insight into mechanisms of hypoxic-ischemic brain injury and, hence, recovery [31, 33]. The ideal time window for prognostication using diffusion MRI is 2–5 days after cardiac arrest: When comparing MRI in this time window to neurological examination at 3 days, diffusion MRI improved the sensitivity for predicting poor outcome by 38%, while maintaining 100% specificity [32]. Interestingly, when combining diffusion MRI with serum NSE, ADC-based predictions identified an additional 5 poor outcome patients out of 14 with 48-h NSE levels less than 78.9 µg/l [34], again illustrating the importance of a multimodal approach for the prognostication of comatose cardiac arrest patients.

Auditory Evoked Potentials

The frontal cortex network of auditory discrimination is emerging as a valid tool to assess cognitive function and recovery in humans with neuropsychiatric and neurological diseases [35]. This auditory-frontal cortical deficiency can be objectively measured with the so-called mismatch negativity (MMN). Fischer et al. first reported the value of MMN in comatose cardiac arrest patients not treated with therapeutic hypothermia [36]. When performed after the acute phase, on average at 10 days from cardiac arrest, all patients in whom SSEP or auditory evoked potentials were abolished did not awaken (100% specificity). More importantly however, all patients in whom MMN was present did wake (100% specificity); therefore, MMN was superior to SSEP for the prediction of awakening and had the best specificity and positive predictive value for good recovery. Our group recently focused on the prognostic value of automated auditory discrimination and MMN in 30 comatose cardiac arrest patients treated with therapeutic hypothermia in whom evoked potentials were performed at two time points (during and after therapeutic hypothermia). All patients (11/30) who displayed an early improvement in auditory discrimination across the two recordings regained consciousness [37].

Conclusion

Prognostication of coma after cardiac arrest and therapeutic hypothermia requires a multimodal approach. Neurological examination remains the first step: Motor response may be delayed up to 5 days after cardiac arrest because of the therapeutic hypothermia and may not be sufficient to accurately predict prognosis in all patients. The addition of EEG as a second step improves prognostic accuracy; in particular, presence of an early (within 24 hours from cardiac arrest) reactive EEG background is a good sign whereas a non-reactive or burst-suppressed EEG pattern is an ominous sign. Bilateral absence of N20 on SSEP at 24–48 hours is almost invariably associated with a poor prognosis and is helpful to confirm irreversible coma. Serum NSE at 48–72 hours may be useful to assess the severity of

acute brain damage; however, the cut-off values for poor prognosis are higher in patients treated with therapeutic hypothermia, thus serum NSE should be used only as a complementary tool and never alone. Diffusion MRI and auditory evoked potentials provide new insight into the mechanisms of hypoxic-ischemic brain injury and may improve the prediction of long-term recovery in comatose survivors of cardiac arrest.

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Delayed Neuroprognostication After Cardiac Arrest and Temperature Management

T. Cronberg, J. Horn, and N. Nielsen

Introduction

The majority of patients who reach the intensive care unit (ICU) following a cardiac arrest are unconscious. For the comatose cardiac arrest survivor, the chances for a good neurological recovery diminish with time after return of spontaneous circulation (ROSC). Neurological assessment is usually performed within days after cardiac arrest as a foundation for decisions concerning limitation of care and interventions. The clinical neurological examination is central in prognostication and is usually combined with neurophysiological, neuroradiological and occasionally biochemical investigations to estimate the extent of permanent brain injury. The predictive values of the different methods have been investigated in numerous trials and incorporated into clinical guidelines [1–3].

Treatment with mild hypothermia has been widely implemented as a neuroprotective strategy for cardiac arrest survivors, but may alter the recovery pattern and the predictive value of prognostic markers. Current guidelines do not provide specific instructions on how to evaluate hypothermia-treated patients but recommend delayed prognostication [3] based on multiple instruments [1]. As a poor prognosis statement usually results in withdrawal of supportive treatment and, subsequently, death of the patient, the method for prognostication clearly has the power to affect the outcome of clinical trials in comatose cardiac arrest survivors.

T. Cronberg
Department of Neurology, Skåne University Hospital, Lund, Sweden

J. Horn
Department of Intensive Care, Academic Medical Center, Amsterdam, The Netherlands

N. Nielsen (✉)
Department of Anesthesia and Intensive Care, Helsingborg University Hospital, Helsingborgs lasarett, 25187, Helsingborg, Sweden
E-mail: niklas.nielsen@telia.com

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This is particularly relevant when blinding is difficult, as with different temperature regimes.

In this review, we discuss how mild hypothermia may affect neuroprognostication, how this issue was dealt with in previous trials of cardiac arrest, and finally we present a novel model for delayed neurological prognostication applied in a large ongoing trial on target temperature management after cardiac arrest, the Target Temperature Management after Out-of-Hospital Cardiac Arrest Trial (TTM)-trial (NCT01020916).

Cardiac Arrest

Out-of-hospital cardiac arrest is a common cause of mortality and morbidity in the western world and in Europe it has an annual incidence of 38 cases per 100,000 inhabitants [4]. Although increased survival from all-rhythm out-of-hospital cardiac arrest has been reported in several studies [5, 6], mortality is still approximately 90 % for the whole group and at least 50 % following hospital admission [7, 8]. Because of a high metabolic ratio and very limited energy reserves, the brain is particularly vulnerable to circulatory arrest and ischemic damage occurs after only a few minutes. Consequently, brain injury accounts for two-thirds of all deaths after admission to the ICU following out-of-hospital cardiac arrest [9] and the majority of survivors suffer some degree of cognitive impairment [10].

Mild Hypothermia

Mild hypothermia to 33 °C has a robust neuroprotective effect in animal models of global ischemia [11]. Following one randomized [12] and one quasi-randomized clinical trial [13] hypothermic treatment has been included in international guidelines as a recommended therapy for patients in coma after cardiac arrest [1]. However, a systematic review of previous trials concluded that the evidence in favor of hypothermia is weak and that earlier trials were associated with substantial risk of potential systematic as well as random error [14].

Neuroprognostication After Cardiac Arrest

A global ischemic brain injury following cardiac arrest manifests itself as persisting coma, myoclonic seizures and loss of brain stem reflexes. Patients who improve their level of consciousness after withdrawal of sedative and analgesic substances usually have a good outcome [15]. For those who remain in coma, the prognosis becomes gradually worse with increasing time from cardiac arrest. Re-

covery of brain-stem functions, such as the pupillary light reflex, corneal reflex and spontaneous breathing usually occurs during the first days after cardiac arrest. This effect is also found in the majority of severely injured patients. Therefore, bilateral lack of pupillary light reflexes or corneal reflexes has a high specificity but low sensitivity for the prediction of a poor prognosis at 72 hours after cardiac arrest [16, 17]. A complete loss of brain stem functions on the other hand might signal complete brain infarction and brain death [18].

Neurological prognostication is usually based on repeated clinical neurological examinations and electrophysiological investigations (electroencephalography [EEG] and somatosensory-evoked potentials [SSEP]). It may be further supported by neuroradiological examinations (computed tomography [CT] and magnetic resonance imaging [MRI]) and biomarkers (neuron specific enolase [NSE] in particular) but the evidence for these methods is less solid [1, 2]. Because the specificity of clinical and neurophysiological findings increases with time, a well-founded judgment of prognosis can usually be made at 72 hours after cardiac arrest in a patient who has not been treated with hypothermia [2, 16]. Hypothermic therapy has been found to make a clinical neurological examination less reliable [19–21], possibly related to increased use [18] and decreased clearance [22] of sedative medication. Delayed neuroprognostication has, therefore, been recommended in patients treated with hypothermia [3].

SSEPs are less sensitive to sedative medication than are EEGs and a bilateral loss of the cortical N20-potential at 24 hours or more after cardiac arrest, predicts a poor outcome with a very high accuracy [17, 23]. The high specificity of SSEP appears to be retained for hypothermia-treated patients if the examination is performed after rewarming, but sporadic false predictions have been reported with SSEP performed during hypothermia [20], and even after rewarming [24]. Furthermore, interobserver variability in the interpretation of SSEPs has been reported [25].

Severely pathological EEG-patterns, including burst-suppression, generalized status epilepticus and α-coma, are associated with a poor prognosis after cardiac arrest. The EEG-pattern is very sensitive to sedative medication and false predictions may therefore occur [2]. The prognostic implications of the supposedly pathological EEG-patterns are not fully known. Specifically, the occurrence of postanoxic status epilepticus has been reported in some patients with good outcome following hypothermia-treated cardiac arrest [26].

Status myoclonus, i. e., generalized myoclonic seizures for more than 30 minutes and usually occurring in facial and axial limb musculature, has been considered a reliable predictor of a poor prognosis if it occurs within 24 hours after cardiac arrest of a primary cardiac origin [27]. After the introduction of hypothermia, survival with good outcome despite early status myoclonus has been reported [28]. A small fraction of cardiac arrest patients develop a total brain infarction with massive edema leading to herniation and may be diagnosed as brain dead [18]. The accuracy of clinical tests to diagnose brain death in cardiac arrest survivors treated with hypothermia has recently been questioned [29].

Neuroprognostication and Outcome of Clinical Trials

The neurological assessment of prognosis following cardiac arrest is critical for outcome because a 'poor-prognosis-statement' often leads to withdrawal of life-sustaining treatment and death of the patient. Early prognostication after hypothermia-treated cardiac arrest is associated with a high rate of false predictions of poor outcome [30]. It has recently been suggested that prognostication that is performed too early may have introduced bias into clinical trials of neuroprotective strategies after cardiac arrest and, thus, may have led to negative results, because a delayed recovery process may have been missed [31].

Neuroprognostication in Previous Cardiac Arrest Trials

The Brain Resuscitation after Cardiac Arrest Trial (BRCT) I [32] and BRCT II [33] studies were conducted prior to the introduction of hypothermia and included comatose adult cardiac arrest patients. BRCT I studied the effects of thiopentone and BRCT II the experimental calcium entry-blocker, lidoflazine. The reports of both studies do not describe any rules for treatment decisions in patients who remained in coma due to severe brain injury. In 1994, Edgren et al. [16] used the 262 patients from the BRCT I study to investigate whether it was possible to reliably predict a permanent vegetative state a few days after cardiac arrest. Variation in treatment of patients who remained in coma existed in this group, as the authors report in the results: "For ethical and economic reasons it was not possible to require indefinite intensive care in the protocol, and local variations in decision making were permitted. Although most patients were given unlimited therapy, some in the Scandinavian centers were changed to intermediate care as early as 2–5 days after cardiac arrest." No further details on treatment limitation or withdrawal were reported.

In 2002, the Hypothermia after Cardiac Arrest (HACA) [12] group and Bernard et al. [13] reported on the positive effects of treatment with hypothermia after cardiac arrest. After enrolment of 275 patients, the HACA study stopped inclusion because of a lower than expected inclusion rate. Of the included patients, 132 died during follow-up. In the manuscript on this study, nothing is described on how decisions on treatment limitations or withdrawal were made. In the Bernard study, active life support was withdrawn from most patients who remained deeply comatose at 72 hours. Patients with an uncertain prognosis underwent tracheostomy and were discharged from the ICU. Of the 84 included patients, 45 died during follow-up. The cause of death was cardiac failure in nine, brain-death was diagnosed in both groups in one patient. The remaining deaths (34) resulted from severe neurologic injury and withdrawal of all active therapy. In the discussion, the authors state "this was always a consensus decision of the treating medical and nursing staff, made in consultation with the family of the patient". Which diagnostic methods were used and how the results of these tests were weighed in treatment decisions is not described.

More recently, a pilot study on the effect of high dose erythropoietin was reported [34]. Nothing is reported about treatment decisions and prognostication in this study. The protocol of the currently ongoing phase III study (clinicaltrials.gov identifier NCT00999583) is not clear about the diagnostics used for prognostication and rules for limitation or withdrawal of treatment.

Is There an Optimal Time-Point for Neuroprognostication After Cardiac Arrest?

Before the introduction of hypothermia as a treatment strategy, relatively strong evidence supported the 72 hour time-point after cardiac arrest as a reasonable moment for prognostication [2, 16]. By this time, the majority of patients with a favorable prognosis will have woken and the risk of a false prediction from clinical findings (absent or extensor motor response to pain, bilaterally absent pupillary or corneal reflexes) or test results (absence of N20-potential on SSEP) will be minimal. Hypothermia appears to have effects on the reliability of the clinical neurological examination and possibly other methods of neuroprognostication as well. Whether this is a result of an altered recovery process or a protracted effect of sedative drugs is not clear. Evidence from further studies will, therefore, need to accumulate until a new algorithm for prognostication after hypothermia-treated cardiac arrest can be formulated.

When therapeutic hypothermia for cardiac arrest was introduced at the Skane University Hospital in Lund (2003), decisions were made to postpone neurological prognostication for patients who remain in coma until 72 h after rewarming to account for a possibly delayed recovery process. In a report of this strategy, 52 % of hypothermia-treated patients awoke before prognostication, 17 % died early and 31 % were still in coma 72 h after rewarming (4.5 days after cardiac arrest) [35]. Only 6/34 patients who were in coma at prognostication awoke at some time-point and 28/34 remained in coma until death. In the majority of the deceased patients, clinical, neurophysiological, biochemical (NSE) and neuroradiological findings supported a massive brain injury and this was confirmed by post-mortem examinations. However, a sub-group of 8/34 patients with low-range NSE (≤20 µg/l) was identified. All examined patients had normal MRI (5/8) and normal SSEPs (6/8). All had a generalized status epilepticus pattern on EEG and a lack of motor or extensor response to pain. Only one patient recovered and with a neurological handicap (Cerebral Performance Category [CPC] 3). Whether more active treatment would benefit the sub-group of cardiac arrest patients with status epilepticus has never been tested in clinical trials, but several authors have reported a prolonged recovery-phase with subsequent good outcome [36, 37], which is in accordance with our own recent experience of four patients (T. Cronberg, unpublished observations).

From a clinical trial perspective, the ideal would be to refrain from prognostication and await the natural course of the postanoxic encephalopathy. However, this

approach has practical and ethical limitations. When prognostication is done at 72 hours after rewarming, i. e., 4 to 5 days after cardiac arrest, almost all patients breathe spontaneously after withdrawal of supportive care and extubation. These patients usually die during the following 1–2 weeks, mainly due to respiratory complications (I Dragancea, personal communication). If a high level of care is maintained and no treatment limitations are implemented, the majority of patients who remain in coma up to several days can be expected to end up in a persistent vegetative state.

Given the uncertainty about the optimal moment after cardiac arrest for prognostication and the serious consequences if the window of opportunity for withdrawal of care is missed, the time-point of prognostication in a modern cardiac arrest-trial needs to be conservative enough to allow recovery of patients and strict enough to avoid unnecessary resource utilization and possible suffering.

The Target Temperature Management Trial

In an attempt to better investigate the optimal target temperature management strategy for comatose survivors after cardiac arrest, the TTM-trial was launched in November 2010. In the trial, outcomes of survival, neurological function and safety are compared for two strict target temperatures of 33 °C and 36 °C for 24 hours after return of spontaneous circulation, with a minimum follow up of 180 days. The sample size will be 850 to 950 patients with cardiac arrest of presumed cardiac origin and according to current inclusion rates, the trial will be finished mid-2013. The aims when designing the TTM-trial were to investigate temperature management in a sufficiently large and general population with two temperature regimes both avoiding fever and where possible sources of bias would be minimized. A standardized and transparent protocol for prognostication and withdrawal of life sustaining treatment was regarded as one of the key components of a low-risk-of-bias trial.

Neuroprognostication in the TTM-Trial

The principles of neurological prognostication for patients enrolled in the TTM-trial have been protocolized [38]. A manual is available and investigators have been instructed concerning principles of prognostication at investigator meetings. The following overruling principles have been adopted:

1. The person who performs the prognostication has to be blinded to the intervention.
2. All patients have to be regarded as if they were treated with hypothermia to 33 °C.
3. Rules for prognostication are to be conservative.

As a general principle, all patients in the trial will be actively treated until 72 hours after the end of the intervention period/rewarming. Neurological prognostication is performed at this time-point or later for all patients who remain unconscious. Earlier prognostication is indicated if: (1) the patient becomes brain dead; (2) the patient has an early myoclonus status; or (3) if there are strong ethical reasons to withdraw intensive care.

In the study protocol, it is defined that: "the neurological evaluation will be based on a clinical neurological examination (including Glasgow Coma Scale [GCS] motor score, pupillary and corneal reflexes), median nerve SSEP and EEG". A conventional EEG is performed in all unconscious patients 12–36 h after rewarming and SSEP at 48–72 h after rewarming at centers where this technique is available. In addition, information from neuroimaging (MRI and CT) may be used but cannot constitute the sole reason for withdrawal of intensive care. Biochemical markers for brain damage should not be used for prognostication for patients included in the TTM-trial. Instead a biobank is collected for later analyses.

One of the following recommendations should be made by the physician performing prognostication:

- Continue active intensive care
- Do not escalate intensive care
- Withdraw intensive care

Findings allowing for discontinuation of life support have been specified in the protocol (Box 1). In the case-record-form, findings from all examinations, recommendations and decisions are recorded.

Box 1

Findings allowing for discontinuation of life support in the Target Temperature Management after Out-of-Hospital Cardiac Arrest Trial (TTM)-trial

1. Brain death.
2. Early myoclonus status[#] (≤24 h from sustained return of spontaneous circulation) and bilateral absence of N20 peak on somatosensory-evoked potential (SSEP) after rewarming.
3. Seventy-two hours after rewarming: Glasgow Coma Scale-motor (GCS-M) score 1–2 and bilateral absence of N20 peak on SSEP performed 48–72 hours after rewarming, or later.
4. Seventy-two hours after end of intervention period: Treatment refractory status epilepticus[*] and GCS-M 1–2.

Generalized myoclonic seizures in face and extremities and continuous for a minimum of 30 min.

* Status epilepticus defined by electroencephalogram (EEG) as sequences (> 10 s) of repetitive epileptiform discharges with an amplitude > 50 μV and a medium frequency ≥ 1 Hz.

constituting >50% of a 30 minute period in a patient with or without clinical manifestations. Treatment refractory, defined as unresponsive to treatment with propofol, midazolam or thiopental for at least 24 h in combination with at least one intravenous antiepileptic substance (including valproate and/or fos-phenytoin) in adequate dose for at least 24 h. Free use of further antiepileptic substances and combinations at the discretion of the attending physician.

Rationale for Prognostication in the TTM-Trial

Despite international and national guidelines, the practice of neurological prognostication and withdrawal of life support varies considerably and may often adhere poorly to recommendations [30, 39]. By strictly regulating the time for prognostication and criteria allowing for withdrawal of life support we aimed to avoid false and premature predictions. The majority of patients with a favorable prognosis will wake up during the first three days after cardiac arrest [16] and we decided to postpone prognostication an extra 1.5 days to account for the effects of sedation during cooling and a possible delay in the recovery process by hypothermia. Recently published studies have showed that although awakening itself may not actually be delayed by hypothermia [40], effects of sedation probably explain why clinical examination at 72 h after the arrest is less reliable after hypothermia-treated cardiac arrest [18]. Clinical examinations may still be unreliable at 4.5 days after cardiac arrest and data supporting this time-point are admittedly scarce. Therefore, an extensor or absent motor response to pain at 4.5 days must be combined with absent SSEPs or treatment refractory status epilepticus to allow for withdrawal of life sustaining treatment in the TTM-trial and, if any of these two conditions, is not fulfilled, at least an extra day of observation is demanded.

We have defined minimal therapeutic efforts to define status epilepticus treatment as refractory, but we recognize that there may be potential for recovery in some patients if more aggressive treatment and/or a longer observation time are allowed. Clearly, this is an area where more knowledge is urgently needed. Moreover, the TTM-protocol defines when withdrawal of life sustaining treatment is allowed but the decisions are made by the treating physician and continued intensive care is always an option.

Most intensivists would consider it unethical to continue intensive care in a patient with generalized myoclonus after cardiac arrest, but false predictions may occur from status myoclonus both with and without hypothermia [28]. To solve this dilemma, we combined early myoclonus status with another strong predictor, SSEP, and allowed for SSEP to be performed earlier in patients with status myoclonus, immediately after rewarming. Early prognostication is also allowed for the small fraction of patients who become brain-dead and they should be diagnosed according to national legislation. However, we recommend that the clinical diagnosis of brain death should be avoided during the first 24 hours after resuscitation and that radiological evidence of herniation and loss of intracerebral blood flow is

sought when there is any doubt about the diagnosis to avoid misdiagnosis [29]. Finally, strong ethical reasons for early withdrawal of care may include generalized malignant disease or a clearly stated wish not to be resuscitated. Such reasons may become evident only after the patient has arrived in the ICU.

Several recently published reviews deal with the issue of neuroprognostication after cardiac arrest in the era of hypothermia treatment [41–43] and detail the reliability of individual prognostic instruments. From the large amounts of comparative data in the TTM-trial, we will be able to learn how different prognostic instruments are affected by cooling. Until we learn more, it is the authors' opinion that a reasonable clinical praxis is to delay prognostication and to avoid decisions to withdraw care based solely on clinical findings and use the model outlined in Box 1. In our experience, such an approach has not resulted in patients with chronic vegetative state [35].

Conclusion

Timing of neuroprognostication and decisions on further life-sustaining therapies are crucial for outcome after cardiac arrest. Hypothermia and concomitant sedation make a clinical neurological examination less reliable even at 72 h after cardiac arrest. We therefore recommend postponing neuroprognostication further until at least 72 h after rewarming and in the proposed model a liberal use of adjunctive methods to support a decision on withdrawal of intensive care is advocated. In the model, the EEG has a central role to diagnose and adequately treat status epilepticus, while SSEP may be used to allow for earlier withdrawal in patients with status myoclonus or confirm poor prognosis at 72 h after rewarming. Neuroimaging is not a part of the model other than to give further support for a clinical diagnosis of brain-death. The role of biomarkers for neuroprognostication after cardiac arrest is currently unclear but a large biobank is being created within the TTM trial. In future cardiac arrest trials, it is imperative to protocolize timing and methods for prognostication to avoid possible bias and imbalances among study groups.

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