Chapter 8

Prognostication in Post Cardiac Arrest Patients Treated with Therapeutic Hypothermia

Ashok Palagiri, Farid Sadaka and Rekha Lakshmanan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55496

1. Introduction

There are over 300,000 out-of-hospital cardiac arrests (OHCA), and 200,000 in-hospital cardiac arrests (IHCA), annually in the U.S. alone. Of these, the survival rate is only 6.4% and 17% respectively (1). Sasson et al. reviewed 75 studies of OHCA, including over 140,000 patients, and found that the pooled survival rate to hospital admission was only 24%, and pooled survival to hospital discharge was only 7.6% (2). Also noted, via the Get With The Guidelines Registry (GWTG-R), was that the rate of survival to hospital discharge after IHCA was 18% for ventricular fibrillation and pulseless ventricular tachycardia, 12% for pulseless electrical activity (PEA), and 13% for asystole (2). During and post cardiac arrest, patients undergo profound systemic ischemia followed by reperfusion. This leads to what is now known as post cardiac arrest syndrome (PCAS), which is comprised of four entities: brain injury, myocardial dysfunction, ischemic/reperfusion response, and the precipitating disease (3). As many as 30% of cardiac arrest survivors will suffer from permanent brain injury (4). The percentage of survivors from the initial cardiac arrest, that subsequently die, is fairly comparable around the world, around 65-75%. Most of these patients die within the first month after return of spontaneous circulation (ROSC). Although the components leading up to survival from cardiac arrest are very important (early access, early CPR, early defibrillation and early advanced care), the main entity that limits ultimate recovery is brain injury from hypoxia. This chapter is mainly concerned with the post cardiac arrest brain injury that occurs and how to prognosticate its recovery. The only treatment that has been proven to improve mortality and neurological outcome is therapeutic hypothermia (TH). Before the utilization of therapeutic hypothermia, many of these post cardiac arrest survivors succumbed to anoxic brain damage (5). As therapeutic hypothermia continues to become standard practice across the world for post cardiac arrest patients, the new question that arises is when and how best to prognosticate both the survivors and non-surviovors of therapeutic hypothermia.Multiple studies have shown that prognostication within 24-48 hrs

after rewarming from TH, does not provide reliable resuts (3). In this chapter, we will review the background of prognostication in comatose patients after cardiac arrest, realizing that these recommendations were all made using studies that did not include patients treated with therapeutic hypothermia. It is fundamental to understand the history of prognostication, in order to appreciate the changes that are needed with the advent of therapeutic hypothermia. The remainder of the chapter will review the most recent literature available regarding prognostication of post cardiac arrest victims having undergone therapeutic hypothermia. We will review the utility of the neurological examination, various electroencephalography (EEG) modalities, somatosensory evoked potentials (SSEP's), biomarkers, and bispectral index monitoring for prognostication. Finally we will provide some guidelines for the timeline of prognostication post cardiac arrest and which methods will provide the best results.

2. Prognostication

When we talk about prognostication with regards to comatose survivors post cardiac arrest, we are looking for tools that are both reliable and accurate. In order to help families determine how best to take care of their loved ones, the literature shows that it is difficult to determine which patients will have fully functional outcomes, as this may takes weeks, to months, to years. What is more helpful is to provide families with information regarding situations where there is no chance of functional recovery with data that is fairly robust. With this type of situation, we are looking for studies and modalities that achieve a false positive rate (FPR) equal to or very closely approaching zero (6). It is known that many patients that survive their initial cardiac arrest event tend to have impairment of their consciousness (7). Many, if not all, of these patients require intensive care. Those that sustain the most damage require the most resources. Because of this situation, strain is added to an already frail healthcare system. Thus, it is paramount to develop guidelines that allow for better prognostication post cardiac arrest, in order to guide both physicians and families with regards to appropriate care for their loved ones. Studies have shown that prognostication plays a significant role in withdrawal of life supporting measures for families and physicians. Keeping all this in mind, one must pay attention to the definition of good and bad outcome that each study has chosen to use. In the studies discussed throughout this chapter, most used either the Glasgow Outcome Scale (GOS) or the Glasgow Pittsburgh Cerebral Performance Categories scale (CPC) (see Table 1). Some studies used the modified Rankin Scale. Table 1 differentiates the three outcomes scales. In basic terms, outcome can be broken down into three groups: 1) survival or death, 2) presence or absence of consciousness, and 3) with or without return to normal social activity. Depending on how authors define outcome in their studies, the CPC/GOS categories they use to define 'poor' outcome will vary (8). In many studies, poor outcome ranges between inability to be independent of activities of daily living (ADL) for a few months, to persistent coma/vegetative state, to death (9). Meadow et al. showed that patient.'s chances of survival decreased the longer they stayed in the ICU.Surprisingly, they also found that even in patients with unanimous predictions of death for > 3 days, 12% of patient's survived (10).

	Glasgow Outcome Scale	CPC*	mRS**
Dead	1	5	0
Comatose or Vegetative	2	4	1,2
Severe Disability (Conscious but Disabled)	3	3	3,4
Moderate Disability (Disabled but Independent)	4	2	5
Good Recovery	5	1	6

*cerebral performance category
**modified Rankin Score

Table 1. Glasgow Outcome Scale; CPC*; mRS**

In order to understand the newest prognostication literature, one must have an understanding of from where the current guidelines stem. In 1981, Levy et al. developed an algorithm, which was the mainstay for prognostication for many years (11). The algorithm basically assured no chance of good recovery if a patient had absent corneal or pupillary reflexes at any time after cardiac arrest, or motor response no better than extension at 72 hrs post cardiac arrest. The algorithm that Levy et al. provided us with in 1981 was replicated in 2012 by Greer et al. and produced similar results (12). As did Levy et al., Greer et al. collected clinical data on days 0, 1, 3, and 7, on nontraumatic coma patients in the emergency department, neuro ICU, medical ICU and cardiac ICU. These algorithms are fundamental to understanding prognostication and the neurological examination. Both of these studies have shown that the clinical neurological exam is necessary for determining prognosis in nontraumatic coma, however, it would be helpful if these algorithms were specific to therapeutic hypothermia patients. Greer et al. plan to perform a subgroup analysis from their data specific to TH patients, which should shed some light on this area.

The current guidelines being used were produced in 2006 by the American Association of Neurology (AAN) (13). The 25 years between the algorithm of Levy et al. and the 2006 AAN guidelines, provided ample amounts of research studies, most of which suggested that the neuro exam should be complemented by ancillary tests. The AAN guidelines can be summarized as follows: 1) Patients with absent corneal reflexes or absent papillary reflexes, or no better than extension motor responses, 3 days after cardiac arrest, have a poor prognosis, 2) Patients with myoclonus status epilepticus within the first 24 hrs of ROSC have a poor prognosis, 3) Patients with burst suppression on EEG, or generalized epileptiform discharges are predicted to have a poor prognosis, 4) Patients with bilaterally absent N20 response on SSEP's, between 24 to 72 hrs post cardiac arrest, have a poor prognosis, and 5) Patients with serum levels of neuron specific enolase (NSE) > 33 ug/L between 24 to 72 hrs post cardiac arrest have a poor prognosis. Unfortunately, the AAN guidelines were being written at the same time that the landmark TH articles were coming out, thus providing us with guidelines that did not incorporate therapeutic hypothermia.

They did, however, include in the guidelines a recommendation that once hypothermia became standard of care, the guidelines would need revision. There does not appear to be one single criterion that can invariably predict poor prognosis (14). Hence the need exists for a multimodality approach to prognostication. Table 2 summarizes the salient points of the 2006 AAN guidelines for prognostication.

Neuroclinical Exam	
Strong evidence (Level A)	The prognosis is invariably poor in comatose patients with absent pupillary or corneal reflexes, or no better than extensor motor responses, at 3 days after cardiac arrest
Good evidence (Level B)	Myoclonic status epilepticus within 24 hrs of primary circulatory arrest has a poor prognosis
Electrophysiological Studies	
Good evidence (Level B)	Bilaterally absent cortical SSEPs (N20 response) between days 1 to 3, can guide a poor prognosis
Weak evidence (Level C)	Burst suppression or generalized epileptiform discharges on EEG predict poor outcomes but with insufficient accuracy
Biomarkers	
Good evidence (Level B)	Serum NSE levels > 33ug/L at days 1 to 3 post cardiac arrest accurately predict poor outcome
Insufficient evidence	Inadequate data exists to support or refute the use of S100-B or CKBB for prognostic value
Insufficient evidence	Inadequate data exists to support or refute the use of ICP monitoring for prognostic value

Table 2. Summary of 2006 AAN Guidelines for Prediction of Outcome in Comatose Survivors After Cardiopulmonary Resuscitation

Another important aspect regarding many of these prognostication studies entails the 'self-fulfilling' prophecy (14). These trials have a common bias that is often seen in prognosis determining trials, in which early withdrawal of support occurs in patients who present with certain findings that have previously been associated with poor prognosis. This makes it very hard to determine the appropriate amount of time to wait post TH, in order to achieve a FPR of zero for various modalities.

Perman et al. performed a retrospective review of charts from two academic hospitals, and found that more than half of the comatose survivors of cardiac arrest were assigned the prognosis of 'poor' by their physicians (1). It was also shown in this review that there exists a large variation in the timing of determining prognosis and in the modalities used to make this determination. It should also be noted that in this study, the use of the term 'poor' prognosis was found in many patients even before the TH protocol was completed. The placement of the term 'poor' prognosis into a patient's chart can have a domino effect on the

opinions of other medical personnel, and should only be used once objective data has been found. This study provides a great example of why specific guidelines regarding timing and modalities for prognostication in post cardiac arrest patients, who have undergone TH, is of paramount importance.

Oddo et al. performed a prospective study looking at clinical criteria that may help predict outcome in comatose survivors of cardiac arrest having received therapeutic hypothermia (15). This study suggested that patients that take longer to regain ROSC after cardiac arrest, even when treated with TH, have worse outcomes. Another smaller study by Wolff et al. found that patients reaching their target temperature quicker, along with those patients who started at a lower temperature, had better short term neurological outcomes post TH. In 2012, a group created the CASPRI (Cardiac Arrest Survival Postresuscitation In-Hospital) score. This group utilized the GWTG-R, and assessed patients that survived IHCA using prearrest CPC scores (16). This study utilized approximately 28,000 patients for the derivation cohort and approximately 14,000 patients for the validation cohort. The CASPRI score utilizes age, initial arrest rhythm, prearrest CPC score, location, duration of resuscitation, and preexisting organ dysfunctions, to predict favorable neurological survival. This simple prediction tool can be used to help facilitate discussions with families, especially in those patients with relatively high scores suggestive of poor outcomes. Unfortunately, this study did not evaluate the use of TH, and hopefully the study can be replicated using only patients that have undergone TH, as that is now the standard of care. This study found that patient factors played little role in outcome, however factors surrounding the cardiac arrest – duration, initial rhythm, and defibrillation time – were very strong predictors of outcome.

Samaniego et al. prospectively studied 85 post cardiac arrest patients, 53 of whom underwent therapeutic hypothermia (17). They found that the patients undergoing TH were more likely to have received sedative agents around the 72 hr post cardiac arrest mark, as opposed to the non-TH patients. Of the six different findings tested, absent corneal reflexes at 72 hrs, no better than extensor posturing at 72 hrs, and peak serum NSE >33 ug/L at any time within 72 hrs, each failed to accurately predict poor outcome. On the other hand, status myoclonus epilepticus within 72 hrs, absence of pupillary response at 72hrs and absence of N20 response after 72 hrs, all accurately predicted poor outcome. It becomes very clear that the amount of medications used to perform TH will also complicate prognostication, since all six findings were able to accurately predict poor outcome in patients that did not receive any sedation. Keeping in mind that TH affects drug metabolism and clearance, Fukokua et al. found that there was a five-fold increase in midazolam levels in TH patients compared to normothermic patients (18). It is also known that propofol concentrations can increase up to 30% in hypothermia treated patients, and fentanyl clearance also decreases significantly. All of this goes to show that one needs to be very mindful of the types and amounts of analgesia, sedation and neuromuscular blockade agents given to TH patients, along with the amount time passing since complete discontinuation of these medications, when attempting to perform prognostication on these patients.

3. Neuro exam

Al Thenayan et al. in 2008 reviewed 282 charts, and found 37 patients that fulfilled the criteria of patients having survived cardiac arrest and having undergone TH(19). They reviewed neuro exam findings for 6 days post cardiac arrest. This study found that motor response no better than extensor posturing at 72 hrs was not a reliable predictor of poor outcome. It also found that while absent corneal reflexes had a FPR of zero, motor responses no better than extension had a FPR of 14%. In 2007, Yannopoulos et al. published a case series of four patients that provided evidence that predictions based on neuro exam alone are insufficient before 72 hrs (20). In their review, these four patients were determined by a board certified neurologist to have poor neurological outcome, at the time of rewarming. At time of discharge, which was over 72 hrs post cardiac arrest, three of the four patients regained full consciousness, and the remaining patient achieved a GCS of 10 (from 6). A retrospective chart review of patients between 2005-2009 by Rittenberger et al. analyzed both TH and non-TH patients, and looked at clinical examination at admission, 24 hrs and 72 hrs post admission (21). The results of this review showed that the neuro exam was definitely not sufficient to make prognostication at 24 hrs. However, at 72 hrs post arrest, the absence of corneal or pupil responses was highly predictive of poor outcome. This was true for both TH and non-TH patients. In the Post-Cardiac Arrest Care 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care (6), it has been written that no study had shown that any neuro examination findings were able to predict poor outcome in less than 24 hrs after cardiac arrest. A review was performed by Oddo et al. in 2011, which discussed various studies and their findings (22). Rossetti et al. showed that TH provided discrepant results with regards to neurological exam findings, when compared to the guidelines suggested by the 2006 AAN paper. In the study by Rossetti et al. there was a FPR of 24% for motor response no better than extension, 4% FPR for absent brainstem reflexes, and 3% FPR for myoclonus. Other studies have also shown FPR's > 0% when looking at motor responses no better than extension. Oddo et al. made recommendations to wait 5-6 days post cardiac arrest and ROSC, before prognostication, as both TH and the medications used during TH can cause elevated FPR's. They also recommended to not rely on motor reactions alone. From the paper by Blondin et al. it was very clear that sedation and neuromuscular blockade used during TH make the clinical exam unreliable (14). Usually these medications are weaned, but some sedatives and analgesia are continued for more than 72 hrs post cardiac arrest. These medications can confound the clinical exam as hypothermia decreases renal and hepatic clearance of these drugs, leading to higher serum levels and prolonged effects. Blondin et al's review paper found that corneal and papillary light reflexes appeared to retain their predictive value at 72 hrs post cardiac arrest in TH patients. Although there are studies that have shown an FPR of 0% when dealing with absent pupillary response at 72 hrs post cardiac arrest with TH there have been cases where patients with absent corneals and poor motor responses did regain consciousness. From the evidence that Blondin et al. reviewed, their recommendations were that absent corneal reflexes and absent pupillary reflexes at 72 hrs are better for poor prognostication, but should not be used alone. They also stated that poor motor response was not effective at predicting poor outcome at 72 hrs. We have now seen that Al Thenayan,

Rossetti, and Blondin et al., agree that the neurological exam alone is not sufficient to reliably prognosticate post cardiac arrest patients treated with TH. On the other hand, Fugate et al. performed a prospective study, which contradicts this viewpoint(23). This study showed that the majority of cardiac arrest survivors (91%), who were treated with hypothermia and regained consciousness, did so within the first three days post cardiac arrest. Of course, when looking closely at the study, the range did vary from two to eight days for regaining of consciousness, which always makes one hesitate to fully prognosticate within a set amount of time. This paper by Fugate et al. does suggest that therapeutic hypothermia does not delay awakening, in cases where there are no confounding variables. When we talk about confounding variables, we are mainly alluding to sedation, analgesia and neuromuscular blockade. It is clearly shown in studies that when sedatives are used in TH, the FPR of poor neurological exams increases. As described earlier, the inclusion of patients in these studies that undergo withdrawal of life sustaining therapies becomes a self fulfilling prophecy, in the sense that delayed awakenings of these specific patients will go unrecognized. With regards to scores that utilize the neuro exam, the mainstay that has been used is the Glasgow coma scale (GCS). Recently, a more comprehensive score has been developed, known as the FOUR score – Full Outline of UnResponsiveness. Fugate et al. utilized this score to determine if it was able to predict outcome in patients after cardiac arrest (24). They assessed both TH and non-TH patients. For all comers in this study, the majority of patients that scored > 8 on their FOUR score, on days 3-5 post cardiac arrest, survived to discharge. They found similar if not better sensitivity and specificity when compared to GCS prognostication.

4. EEG

Walker et al. showed that close to one out of every twelve normothermic comatose ICU patients had nonconvulsive status epilepticus(25). It has also been shown that up to 44% of post cardiac arrest patients can suffer from seizures (26). In a case report by Hovland et al., they described a 53 year old female suffering from an OHCA secondary to STEMI, who underwent TH (27). Almost 90 hrs after admission, and after analgesia, sedation and NMB's were weaned off, the patient exhibited status epilepticus on EEG. After day 17, the patient was able to dress herself. She required multiple AE's during her admission to control her SE, which may have been recognized earlier had continuous EEG monitoring been used. This case report, and other studies, stresses the importance of monitoring post cardiac arrest patients undergoing TH for seizures. Utilizing EEG post cardiac arrest allows us to evaluate how much of the cortex has been damaged. Ongoing brain damage may occur as seizure activity leads to neuronal necrosis and apoptosis. The 2006 AAN guidelines stated that epileptiform complexes on a flat background, burst-suppression pattern with generalized epileptiform activity/periodic, or generalized background suppression less than 20 uV, seen within 3 days of cardiac arrest, predicted poor outcome with a FPR of 3% (22). However, as stated earlier, these guidelines were with respect to patients that had not undergone TH. It should be known that there are a few common EEG findings seen after cardiac arrest (14). These patterns include extremely low voltage, continuous, discontinuous burst-suppression, and electrographic status epilepticus with recurrent epileptiform activity. In addition, the

use of TH can also cause very low voltage EEG backgrounds, which may be due in part to neurogenic medications. Of the various coma patterns that can be seen post cardiac arrest, burst-suppression patterns with little or no reactivity carry the worst prognosis (28). Alpha coma patterns can be seen in 10-15% of patients suffering from anoxic brain injury. Another important aspect of the EEG is the reactivity that can be seen when evaluating patients. This reactivity correlates with the activity of the reticular activating system. One can determine reactivity by providing a noxious stimulus and noting the reactivity of the EEG pattern. This aspect of reactivity will be discussed later in the chapter. The American Heart Association has recommended an early one-time EEG or continuous EEG monitoring to look for seizures in TH patients post cardiac arrest. The reason for this is due to clinical seizures being obscured by neuromuscular blockade or high doses of sedatives. It should also be recognized that seizures during TH can be mistaken as shivering (27). Prior animal studies have shown that TH is protective against seizures, and Orlowski et al. (29) and Corry et al. (30) have shown that TH can be used to successfully treat seizures in adult and pediatric patients alike. One of the proposed mechanisms for this protective effect is that hypothermia increases the epileptogenic threshold, making it more difficult for seizures to occur. On the one hand, although therapeutic hypothermia and sedative therapy may protect against seizures, the use of neuromuscular blockade may mask seizures and hamper their diagnosis and treatment (26).

There have been multiple different grading scales proposed with regards to EEG in order to help predict the outcomes of comatose survivors of cardiac arrest (31). Most popular of these was developed in 1965 by Hockaday et al. With this scale, the EEG was divided into 5 distinct grades. The grades were based upon both the dominant frequency of the EEG and whether unfavorable patterns were present. It has since been shown that unfavorable patterns on EEG correlate with poor prognosis. As stated earlier, the patterns seen most frequently to correlate with poor prognosis are burst suppression and electrocerebral silence. Studies have shown that comatose survivors of cardiac arrest, who initially have poor EEG grades, eventually shift to better EEG grades over time. This presents an important component of EEG monitoring, in which the changes are dynamic, and can progress either favorably or unfavorably over time. In the past, one of the most agreed upon poor prognosis EEG patterns, when present greater than 24 hrs post cardiac arrest, was electrocerebral silence. It should be known that this is very difficult to achieve in an ICU setting due to electrical interference from multiple sources. This being said, when electrocerebral silence is present, it is very significant for poor prognosis. Unfortunately, the data regarding electrocerebral silence comes from pre-TH studies.

When evaluating the EEG findings in TH patients, one can divide the patterns into malignant, benign and uncertain (9). When discussing malignant patterns, we are mainly concerned with suppression, burst suppression, nonreactivity, and generalized periodic complexes. The difficulty with using EEG consistently throughout ICU's is the lack of a consistent classification system and the lack of consistency regarding how soon and how frequent EEG's should be performed post cardiac arrest. Many times after anoxic injury, periodic patterns such as periodic lateralized epileptiform discharges (PLEDs) and bilateral independent lateralized epileptiform discharges (BiPLEDs) are seen on EEG (28). It is

important to be able to differentiate between these periodic epileptiform patterns and actual seizures, as intensive treatment of seizures can improve patient outcomes. When reviewing the EEG patterns, one must make sure that there are no concomitant medication effects. Sufficient time after cessation of medications should be given before using EEG changes for prognostication. Since as many as 44% of post-cardiac arrest patients can suffer from seizures, it becomes hard to tell whether seizures are the contributing factor of poor prognosis, or if the seizures are markers of irreversibly damaged brains (32). Mani et al. retrospectively looked at 38 comatose post cardiac arrest patients that underwent TH, and found that those patients that exhibited seizures did so within 24 hours. Many of these patients had their seizures during the maintenance phase of TH. The seizures were refractory to treatment and associated with poor short term neurological outcome. From this study, not only did it suggest that early epileptiform activity can help with prognostication of comatose post cardiac arrest patients in the first 24-36 hrs post arrest, but also suggested that early monitoring of these patients for seizure activity is a necessity. It should be noted that the incidence of seizures in post cardiac arrest TH patients is probably underestimated as many of the medications used for TH have antiepileptogenic properties. A small study by Rossetti et al. looked at six patients that developed post anoxic status epilepticus (PSE) after cardiac arrest and treatment with TH, who eventually improved beyond a vegetative state (33). PSE is comprised of prolonged myoclonic or convulsive seizures or nonconvulsive status epilepticus. This study suggested that when these patients retain their brainstem reflexes, cortical SSEP, and background reactivity (will be discussed in later paragraphs), PSE can be associated with improvement beyond a vegetative state. In another study by Legriel et al., 19 out of 51 patients treated with TH exhibited myoclonus (26). As has been reported in the past, patients that are rewarmed too quickly may develop rebound seizures, and this may have been the case in this study. There were also five patients in this study that developed electrographical status epilepticus (ESE), and all five passed away. This is consistent with prior studies showing poor prognosis in patients post TH exhibiting ESE. In these five patients, the ESE was very recalcitrant to antiseizure therapy. Once again, this study provided more evidence that seizures may be masked by medications used with TH, which was most likely neuromuscular blockade in this study.

When using EEG in post cardiac arrest patients treated with TH, the question arises whether to use continuous (cEEG) monitoring versus spot monitoring. A few studies will be discussed that show positive findings in support of continuous monitoring. Cloostermans et al. looked at 56 patients having undergone TH post cardiac arrest (34). They found that of the 29 patients that had poor outcomes, those with CPC scores between 3-5 all died. This study utilized continuous EEG monitoring on the patients, and found that prognostication could be differentiated by analyzing whether the patient had a continuous pattern on the EEG or low voltage, isoelectric, or burst suppression patterns. Those patients that succumbed in this trial did not display continuous patterns on their cEEG. Rossetti et al. looked at 34 post cardiac arrest TH patients receiving cEEG monitoring (35). They found that the survivors in this study, all 19 out of 34, had reactive backgrounds. As stated earlier, this can be elicited with a noxious stimulus during cEEG, and observing the background activity. Nonreactivity of EEG background in this study was predictive of 100% mortality. Rossetti et al. studied 111 consecutive TH treated comatose patients, and found that

unreactive EEG background was a strong and independent risk factor for poor prognosis and mortality (5). One important factor that makes this study stand out from others is that it was exempt from the 'self-fulfilling prophecy'. Background EEG reactivity was not part of the decision making process of the physicians managing these patients, thus proving reactivity to be robust prognosticator. What may be of even more use in the era of TH is the use of amplitude integrated EEG (aEEG). aEEG is simple to apply in critical care patients and also easy to learn how to read. Rundgren et al. conducted studies in 2006 and 2010 utilizing aEEG. In 2006, they showed that all patients with continuous pattern on aEEG regained consciousness. Those with mixed patterns (continuous and discontinuous) did not all regain consciousness (36). The 2010 study was a prospective observational study in which they assessed 95 patients treated with TH post cardiac arrest with both EEG and aEEG (37). The underlying need for this study stemmed from previous evidence showing that TH patients often receive sedatives, analgesics, and muscle relaxants, whose effects are prolonged due to TH itself. It is known that TH decreases the metabolic rate of the body and the clearance of these drugs. Because of this effect, TH patients do not have a reliable exam during the first 24-72 hrs post cardiac arrest. In studies that claim to be able to prognosticate based on the neurological exam within the first 24 hrs, one must take into consideration that these patients may have received less neurogenic medications. With the use of these medications in TH patients, as written earlier, clinical seizures may be masked. In this study by Rundgren et al., continuous EEG pattern was defined as a pattern showing continuous cortical activity, with delta and/or theta and/or alpha frequency waveforms in the original EEG. In this study, patients that started out with, or developed into, a continuous EEG pattern had a higher propensity to recover their consciousness. They also found that patients exhibiting a burst suppression pattern at any time during their monitoring were more likely to succumb to death or continue their comatose state. In this study, having or developing a continuous pattern on EEG/aEEG during therapeutic hypothermia has a PPV of 87-91%. The reason flat EEG/aEEG pattern was not associated with a poor prognosis in this study, was due to 3 patients recovering neurological function with flat aEEG patterns. All 22 patients exhibiting burst suppression pattern at any time during their admission on their EEG either remained unconscious or passed away. In this study, ESE was observed in 27% of the patients. It has been described in the literature that postanoxic status epilepticus has mortality rates that are close to 100%. The patients with ESE that recovered consciousness showed that the ESE arose from a continuous background, which possibly suggests that a continuous background portends to a favorable prognosis, even if ESE arises from it. Lastly, myoclonic status epilepticus (MSE) is a common finding post cardiac arrest (14). It appears clinically as either spontaneous or constant myoclonus. Various studies have found conflicting results, with some patients never regaining consciousness after MSE, and others actually regaining consciousness. From these findings, MSE can not be used to invariably predict poor prognosis.

5. SSEP

The second electrophysiological application that has shown usefulness in prognostication for post cardiac arrest TH patients is somatosensory evoked potentials (SSEP). SSEP consists

of a series of waveforms and reflects neural structures. SSEP recordings are noninvasive and can be easily recorded at the bedside in ICU settings (38). Normally, SSEP requires a stimulus that provides an ipsilateral thumb twitch. With the use of TH and the concomitant muscle relaxants used, the intensity of the stimulus needs to be stronger, such that an ipsilateral supraclavicular response is elicited, as opposed to the normal ipsilateral thumb twitch. There are three main stimulation 1 sites to elicit SSEP: median nerve at wrist, common peroneal nerve at knee, and posterior tibial nerve at the ankle. Abnormal SSEP's can signify dysfunction at various points along the neural axis, including peripheral nerve, plexus, nerve root, spinal cord, brain stem, thalamocortical projections, and primary somatosensory cortex. With regards to post cardiac arrest brain injury, SSEP's are used to mainly evaluate the latter three. SSEP's are noted by their deflection and their latency, where positive deflection is denoted as P and negative as N. The number following the deflection notation signifies the latency of the evoked potential. When dealing with prognostication, the objective of SSEP is to determine if there will be return of cerebral function. The N20 peak is felt by most to represent the hand area of the somatosensory cortex. It originates in the posterior bank of the central sulcus and is not influenced by drugs and metabolic derangements.

With regards to TH and the median nerve N20 response, more studies are being published each year, proving its utility. Prior to these studies, the AAN guidelines stated that bilateral absence of median nerve N20 response between 24 to 72 hrs post cardiac arrest accurately predicted poor outcomes. In 2010, the AHA post cardiac arrest care guidelines stated the same, for patients greater than 24 hrs post cardiac arrest; however, both of these guidelines were based on non-TH studies. These findings were confirmed by Zandbergen et al. in their own analysis in non-TH patients, from which they recommended that outcome predictions be made at least 72 hrs after onset of coma. (28). In 2000, Rothstein et al. performed a meta-analysis of 16 studies, covering 572 patients (39). Of these, 229 patients had absent N20 responses, and none of them regained wakefulness. Although multiple studies have shown that absent N20 response is associated with poor outcome, it should be noted that the presence of N20 response does not always correlate with arousal from coma (9). Tiainen et al. performed a prospective, randomized controlled trial, looking at 60 patients, which was a substudy of the landmark European Hypothermia After Cardiac Arrest study in 2002 (38). In this small study of 60 patients, SSEP was compared between TH and non-TH patients. It was found that although TH increases the latency of the median nerve SSEP, the N20 SSEP is preserved in TH. Fortunately the cortical N20 response is only abolished at a temperature of 20 degrees Celsius. Leithner et al. retrospectively studied 112 post cardiac arrest patients treated with TH and having undergone SSEP testing (40). The SSEP.'s were recorded 24 hrs post resuscitation, and of the 36 patients that had absent bilateral N20 responses, 35 had poor outcomes. One patient recovered and one patient had barely detectable N20 responses. Both of these patients had good outcomes and recovered their N20 responses, which brings up the issue of when SSEP testing is most appropriate post cardiac arrest. In the patient with absent N20 responses and good outcome, the patient had severely prolonged peripheral SSEP's, that were felt due to the patient's underlying alcoholism and peripheral neuropathy.

It should be noted that the reason for these patients having good outcomes may not be due to truly absent N20 responses, but may be attributed to interobserver variability of SSEP readings, where it may be difficult to truly differentiate between absent and severely reduced responses. In 2009, Bouwes et al. performed a prospective multicenter cohort study to determine if absent N20 response during TH remains absent upon rewarming (41). In this study, poor outcome was defined by a GOS of 1-2. Out of 77 patients studied, 56% had poor outcome, and of the 13 patients with absent N20 responses, all had poor outcomes. 10 of the 13 patients with absent N20 response survived to normothermia, and all ten of them retained the finding of absent N20 responses. This small study suggests that utilizing SSEP testing earlier during the TH process may be helpful in prognosticating for families. Although this small study showed that the absent N20 responses are retained after rewarming, it should also be known that the presence of a median nerve N20 response can be lost after cardiac arrest. This is most likely due to post CPR delayed hypo-perfusion. After cardiac arrest, the cerebral blood flow can drop by as much as 50%, which leads to secondary ischemia and necrosis. Thus, initially present N20 responses may vanish when tested > 24 hrs after cardiac arrest. These issues suggest that repeat SSEP testing should be done on post cardiac arrest patients treated with TH. From the literature that is available with the use of TH, it seems apparent that median nerve N20 SSEP testing is a robust tool in prognostication, but once again, should be used in conjunction with other modalities.

6. Biomarkers

With regards to prognostication and post cardiac arrest patients, there are two biomarkers that have been studied the most – neuron specific enolase (NSE) and S100-B. S-100B is a homodimer protein found in glia and Schwann cells that binds calcium (42). It regulates apoptosis, outgrowth, and differentiation of neurons. S-100B is part of the S-100 calcium binding protein family, whose name is derived from the fact that it is 100% soluble in ammonium sulfate at neutral pH. It is known to induce the release of inflammatory cytokines which propagate brain damage. NSE on the other hand is a gamma gamma isomer of enolase. It is a cytoplasmic enzyme of glycolysis, and is released into the blood stream when brain damage occurs via damage to the blood brain barrier. Based on these properties of these biomarkers, it follows suit that decreasing S-100B levels suggest improved outcome presumably due to decreased release of inflammatory cytokines, and rising NSE levels are suggestive of poor outcome due to larger amounts of brain damage. NSE is the most studied of these two biomarkers. The 2006 AAN guidelines stated that serum levels of NSE > 33 ug/L at days 1 to 3 predicted poor outcome, in non-TH treated patients. Cronberg et al. looked at 111 consecutive TH patients in 2011 and found that all 17 of the patients that did not regain consciousness had a NSE > 33ug/L (43). At the same time, in 2011, Blondin et al. provided a review article of the data available from prognostication studies, showing that with the use of TH, the cutoff levels for NSE varied, and the previously accepted level for 33ug/L was no longer valid (14). TH has been shown to decrease NSE levels, which correlates with improved outcomes. Multiple studies have attempted to find a 'one size fits all' cutoff level for NSE, but have yet to be successful,

mainly due to the small number of patients in these studies. Another issue is that NSE levels can be affected by time, laboratory assay, hemolysis, and hypothermia. The one aspect most of these studies have in common is that a rising NSE level in TH patients does correlate with poor prognosis, and may be useful with other modalities to make life support decisions. Wolff et al. showed that patients that had quicker times to achieve goal temperature for TH had lower maximal NSE levels, supporting evidence that has shown that this approach to TH is beneficial to post cardiac arrest patients (44). One study that showed that S-100B may be superior to NSE for prognostication purposes was conducted by Shinozaki et al. in 2009 (42). This multicenter prospective observational study followed blood samples taken immediately after admission, 6hrs post and 24 hrs post cardiac arrest. Bottiger et al. previously showed that post cardiac arrest patients exhibited hourly variation of S100-B (45). Although 80 patients were found eligible for this study, only 45 of them received TH, making this study's conclusions less valid for the current TH atmosphere. What this study showed was that 'poor' outcome patients had rising NSE levels, and steady S100-B levels. Those patients that had 'favorable' outcomes had dropping S100-B levels. Oksanen et al. looked at 90 patients having suffered OHCA due to witnessed ventricular fibrillation, who underwent TH, and found that the formerly accepted cutoff level of < 33ug/L for NSE was only able to predict 'poor' outcome 100% of the time at > 48 hrs post cardiac arrest (46). The cutoff level they found at 24 hrs was higher, 41 ug/L. From the data that this group gathered, they also found that the rise in NSE levels between 24 and 48 hrs could provide a moderate sensitivity for 'poor' prognostication. In 2009, Rundgren et al. studied a group of TH patients for 72 hrs post normothermia and found that a rise of NSE > 2ug/L between hrs 24 and 48 was indicative of poor outcome (47). Almaraz et al. provided a nice review of the current literature available regarding NSE cutoff levels and prognostication (48). They also noticed that there are limited studies available, various factors contribute to difficulty in finding a specific cut-off level for prognostication including different study populations, different definitions of poor outcome, difference in the laboratory assays and the timing of the when the levels are drawn. The range of cut-off values in studies to date range from 25 to 80 ug/L. One of the largest studies to date, by Reisinger et al., which included 227 patients, only had 20 patients that underwent TH, thus making it not applicable to current practices (49). Lastly, it should be known that reasons do exist for falsely elevated NSE levels including any process that destroys cells both intrinsic and extrinsic, as well as seizures (48).

7. Bispectral index

Bispectral index monitoring (BIS) is a processed EEG monitoring tool. It is a statistically based, empirically derived complex parameter that is based on EEG sub parameters. It provides a score between 0-100, where zero is electrocerebral silence and 100 is fully awake. For general anesthesia, the typical goal is 40-60 on BIS monitoring. Stammet et al. looked at 45 patients in 2009 through a prospective, observational, unblinded study, and found that of the 14 patients that had a BIS of zero all had poor CPC scores (50). Although the BIS of zero correlated very well with poor prognosis, there were 16 patients without a BIS of zero, of

which 11 died and 6 had poor neurological outcomes. Seder at al in 2010 looked at 83 TH patients, and evaluated both BIS and suppression ratio (51). Suppression ratio (SR) is the amount of isoelectric activity that is present. Poor outcome in this study was defined as a CPC score of 3-5, and patients that had low BIS values along with high SR values were associated with poor outcomes. Lastly, Leary et al. studied post cardiac arrest patients treated with TH after their neuromuscular blockade was in effect, in order to obtain accurate BIS levels (52). BIS values were taken at the initiation of TH, and at 12 and 24 hrs afterwards. Of the 62 patients studied, 16 of them had a BIS of zero within 24 hrs of TH and all 16 died. These studies suggest that for poor prognostication, BIS values of zero may be useful; however more robust studies are needed for validation.

8. Conclusion

As stated earlier, the parameters found in the AAN recommendations from 2006 were all determined in patients that did not undergo TH. From the literature thus far in the post TH era, the optimal timing for prognostication has yet to be fully elucidated. However, the literature reviewed in this chapter should be used as a new baseline regarding when and how to prognosticate post cardiac arrest patients having undergone TH. It must be recognized that drug clearance is reduced at lower core body temperatures. It should also be recognized that during TH, in order to prevent shivering and decrease cerebral metabolic rate, the use of analgesia, sedatives, and paralytics are standard of care and will delay prognostication due to delayed clearance (1). Friberg and Rundgren et al. have suggested that the neurological exam for prognostication post cardiac arrest be supplemented by at least one other modality, and be performed 72 hrs post arrest (53). The AHA guidelines also recommend that a minimum of 72 hrs should transpire post cardiac arrest and return of spontaneous circulation before utilizing any modalities for prognostication in patients having undergone TH (6). Fugate et al. have shown in their studies that a majority of their patients ultimately wake up by day 3, which poses a question regarding the minority of patients that do not awaken (23). How long should one wait post cardiac arrest and post TH before being able to provide accurate prognostication? It would seem that waiting at least 72 hours post rewarming and 72 hours post cessation of any analgesia, sedation, or neuromuscular blocking agents, is a good start, however, as stated in multiple studies thus reviewed, the neurological exam must be accompanied by at least one other modality. EEG has a robust amount of evidence with regard to prognostication in the post cardiac arrest TH patients (27,34,35). It can be safely stated that EEG should be performed as early as possible post cardiac arrest, and electrographical seizures should be treated aggressively (14). The use of aEEG appears to have a solid place in prognostication of TH treated patients, and is simple modality to adopt in the neurocritical care setting (36,37). Biomarkers such as NSE and S-100B, in the post TH era, do not seem to be able to accurately predict outcome consistently, seen with multiple studies having various cutoff levels for prognostication (48). Finally the possibility exists for BIS monitoring to play a role in early prognostication during hypothermia, but more studies are needed at this time to consider

this technique standard of care (50-52). A concern that arises with setting specific time limits for prognostication is regarding the case reports of patients that have regained consciousness well over 72 hrs post cardiac arrest. When assessing these case reports, the specifics regarding the modalities that were used for prognostication need to be ascertained, in order to take these case reports at their face value. Making changes in guidelines for prognostication based on case reports and/or studies with small numbers of patients can cause significant strain on the healthcare system with little benefit for the patient and their families. Thus, there still needs to be larger, more robust studies, to validate the optimal timing and the various prognostication modalities discussed in this chapter.

Author details

Ashok Palagiri, Farid Sadaka and Rekha Lakshmanan
Mercy Hospital St Louis, Saint Louis University Hospital, USA

9. References

[1] Perman SM, Kirkpatrick JN, Reitsma AM, Galeski DF et al (2012) Timing of neuroprognostication in postcardiac arrest therapeutic hypothermia. Crit Care Med. 40 (3): 1-6

[2] Nolan JP (2011) Optimizing outcome after cardiac arrest. Current Opinion in Critical Care. 17:520-526

[3] Nolan JP, Soar J (2010) Postresuscitation care: entering a new era. Current Opinion in Critical Care. 16: 216-222

[4] Sanfillippo F, Li Volti G, Ristagno G, Murabito P, Pellis T et al (2010) Clinical biomarkers in brain injury: a lesson from cardiac arrest. Front Biosci. 2(1):623-640

[5] Rossetti AO, Oddo, M, Logroscino, G, Kaplan PW (2010) Prognostication after Cardiac Arrest and Hypothermia A Prospective Study. American Neurological Association. 67 (3): 301-307

[6] Peberdy MA, Callaway CW et al (2010) Part 9: Post-Cardiac Arrest Care 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation. 122[suppl 3]:S776-778

[7] Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA et al (2008) Post-Cardiac Arrest Syndrome Epidemiology, Pathophysiology, Treatment, Prognostication A Consensus Statement from the International Liaison Committee on Resuscitation. Circulation. 118:2466-2469

[8] Shonixaki K, Oda S, Sadahiro T, Nakamura M, Abe R et al (2009) Serum S-100B is superior to neuron-specific enolast as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. Resuscitation. 80:870-875

[9] Geocadin RG, Eleff SM (2008) Cardiac arrest resuscitation: neurologic prognostication and brain death. Current Opinions in Critical Care. 14:261-268

[10] Meadow W, Pohlman A, Frain L, Ren Y, Kress JP, Teuteberg W, Hall J (2011) Power and limitations of daily prognostication of death in the medical intensive care unit. Crit Care Med. 39(3):474-479
[11] Mayer SA (2011) Outcome prediction after cardiac arrest. Neurology. 77:614-615
[12] Greer DM, Yang J, Scripko PD, Sims JR, Cash S et al (2012) Clinical examination for outcome prediction in nontraumatic coma. Crit Care Med. 40(4):1150-1156
[13] Wijdicks EFM, Hijdra A, Young GB, Bassetti CL, Wiebe S (2006) Practic Parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (en evidence-based review). American Academy of Neurology. 67:203-210
[14] Blondin NA, Greer, DM (2011) Neurologic Prognosis in Cardiac Arrest Patients Treated with Therapeutic Hypothermia. The Neurologist. 17 (5): 241-248
[15] Oddo M, Ribordy V, Feihl F, Rossetti AO, Schaller MD, Chiolero R, Liaudet L (2008) Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: A prospective study. Crit Care Med. 36(8):2296-2301
[16] Chan PS, Spertus JA, Krumholz HM, Berg RA et al (2012) A Validated Prediction Tool for Initial Survivors of In-Hospital Cardiac Arrest. Arch Intern Med. 172(12):947-953
[17] Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CAC (2011) Sedation Confounds Outcome Prediction in Cardiac Arrest Survivors Treated with Hypothermia. Neurocrit Care. 15:113-119
[18] Fukuoka N, et al. (2004) Biphasic concentration change during continuous midazolam administration in brain-injured patients undergoing therapeutic moderate hypothermia. Resuscitation. 60(2):225-30
[19] Al Thenayan E, Savard M, Sharpe M, Norton L, Young B (2008) Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. Neurology. 71: 1535-1537
[20] Yannopoulos D, Kotsifas K, Aufderheide TP, et al (2007) Cardiac arrest, mild therapeutic hypothermia, and unanticipated cerebral recovery. Neurologist. 71:1535-1537
[21] Rittenberger JC, Sangl J, Wheeler M, Guyette FX, Callaway CW (2010) Association between clinical exam and outcome after cardiac arrest. Resuscitation. 81: 1128-1132
[22] Oddo M, Rossetti AO (2011) Predicting neurological outcome after cardiac arrest. Current Opinion in Critical Care. 17:254-259
[23] Fugate JE, Wijdicks EFM, White RD, Rabinstein AA (2011) Does therapeutic hypothermia affect time to awakening in cardiac arrest survivors? Neurology. 77: 1346-1350
[24] Fugate JE, Rabinstein AA, Claassen DO, White RD, Wijdicks EFM (2010) The FOUR Score Predicts Outcome in Patients after Cardiac Arrest. Neurocrit Care. 13:205-210
[25] Walker MC (2003) Status epilepticus on the intensive care unit. J Neurol. 250:401-406
[26] Legriel S, Bruneel F, Sediri H, Hilly J, Abbosh N, Lagarrigue MH et al (2009) Early EEG Monitoring for Detecting Postanoxic Status Epilepticus during Therapeutic Hypothermia: A Pilot Study. Neurocrit Care. 11: 338-344

[27] Hovland A, Nielsen EW, Kluver J, Salvesen R (2006) EEG should be performed during induced hypothermia. Resuscitation. 68: 143-146
[28] Kaplan PW (2006) Electrophysiological Prognostication and Brain Injury from Cardiac Arrest. Seminars in Neurology. 26(4):403-412
[29] Orlowski JP, Erenbertg G, Lueders H, Cruse RP (1984) Hypothermia and barbiturate coma for refractory status epilepticus. Crit Care Med. 12:367-372
[30] Corry JJ, Dhar R, Murphy T, Diringer MN (2008) Hypothermia for refractory status epilepticus. Neurocrit Care. 9:189-197
[31] Thakor NV (2006) Clinical Neurophysiologic Monitoring and Brain Injury from Cardiac Arrest. Neurologic Clinics. 24:89-106
[32] Mani R, Schmitt SE, Mazer M, Putt ME, Gaieski DF (2012) The frequency and timing of epileptiform activity on continuous electroencephalogram in comatose post-cardiac arrest syndrome patients treated with therapeutic hypothermia. Resuscitation. S116:1-8
[33] Rossetti AO, Oddo M, Liauder L, Kaplan PW (2009) Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. Neurology. 72: 744-749
[34] Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJAM (2012) Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: A prospective cohort study. Crit Care Med. 40(10):1-9
[35] Rossetti AO, Urbano LA, Delodder F, Kaplan PW, Oddo M (2010) Prognostic value of continuous EEG monitoring during therapeutic hypothermia after cardiac arrest. Critical Care. 14:R173:1-8
[36] Rundgren M, Rosen I, Friberg H (2006) Amplitude integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intensive Care Med. 32:836-842
[37] Rundgren M, Westhall E, Cronberg T, Rosen I, Friberg H (2010) Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med. 38(9):1838-1844
[38] Tiainen M, Kovala TT, Takkunen OS, Roine RO (2005) Somatasensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. Crit Care Med. 33(8):1736-1740
[39] Rothstein TL (2000) The role of evoked potentials in anoxic-ischemic coma and severe brain trauma. J Clin Neurophysiol. 17:486-497
[40] Leithner C, Ploner CJ, Hasper D, Storm C (2010) Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? Neurology. 71:965-969
[41] Bouwes A, Binnekade JM, Zandstra DF, Koelman JHTM, van Schaik IN, Hijdra A, Horn J (2009) Somatosensory evoked potentials during mild hypothermia after cardiopulmonary resuscitation. Neurology. 73:1457-1461
[42] Shinozaki K, Oda S, Sadahiro T, Nakamura M, Abe R et al (2009) Serum S-100B is superior to neuron-specific enolast as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. Resuscitation. 80:870-875
[43] Cronberg T, Rundgren M, Westhall E, Englund E, Siemund R et al (2011) Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. Neurology. 77(7):623-630

[44] Wolff B, Machill K, Schumacher D, Schulzki I, Werner D (2009) Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. International Journal of Cardiology. 133:223-228

[45] Bottiger BW, Mobes S, Glatzer R, et al. (2001) Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. Circulation. 103:2694-2698

[46] Oksanen T, Tiainen M, Skrifvars MB, Varpula T, Kuitunen A et al (2009) Predicitive power of serum NSE and OHCA score regarding 6-month neurologic outcome after out-of-hospital ventricular fibrillation and therapeutic hypothermia. Resuscitation. 80:165-170

[47] Rundgren M, Karlsson T, Nielsen N, et al. (2009) Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. Resuscitation. 80:784-789

[48] Almaraz AC, Bobrow BJ, Wingerchuk DM, Wellik KE, Demaerschalk BM (2009) Serum Neuron Specific Enolase to Predict Neurological Outcome After Cardiopulmonary Resuscitation. The Neurologist. 15(1):44-48

[49] Reisinger J, Hollinger K, Wolfgang L, et al. (2007) Prediction of neurological outcome after cardiopulmonary resuscitation by serial determination of serum neuron-specific enolase. Eur Heart J. 28:52-58

[50] Stammet P, Were C, Mertens L, Lorang C, Hemmer M (2009) Bispectral index (BIS) helps predicting bad neurological outcome in comatose survivors after cardiac arrest and induced therapeutic hypothermia. Resuscitation. 80:437-442

[51] Seder DB, Fraser GL, Robbins T, Libby L, Riker RR (2010) The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Intensive Care Med. 36:281-288

[52] Leary M, Fried DA, Gaieski DF, Merchant RM, Fuchs BD, Kolansky DM, Edelson DP, Abella BS (2010) Neurologic prognostication and bispectral index monitoring after resuscitation from cardiac arrest. Resuscitation. 81:1133-1137

[53] Friberg H, Rundgren M (2008) Prediction of outcome after cardiac arrest and induced hypothermia. Abstr. Circulation. 118:S823