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The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest

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Abstract *Purpose:* To evaluate the bispectral index (BIS) and suppression ratio (SR) as very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. *Methods:* Demographic data, BIS1, and SR1 were recorded from 97 patients after the first dose of neuromuscular blockade, with outcomes blinded, and compared to the discharge Cerebral Performance Category (CPC). Receiver-operator characteristic curves and a multiple logistic regression model were constructed to predict good (CPC 1-2, GO) and poor (CPC 3-5, PO) neurological outcomes. *Results:* Fourteen patients were excluded from the final analysis; 33 of the remaining 83 patients (40%) were classified as GO. The BIS1 was higher in patients with GO (37 [28–40] vs. 7 [3–15], $p < 0.001$). BIS1 < 22 predicted PO with a likelihood ratio (LR) of 14.2 and an area under the curve (AUC) of 0.91 (95% CI 0.85–0.98, $p < 0.001$). SR1 ≥48 predicted PO with a LR of 12.7 and an AUC of 0.90 (95% CI 0.83–0.98, $p < 0.001$). Both BIS1 (ΔAUC 0.16, $p = 0.006$) and SR1 (ΔAUC 0.16, $p = 0.005$) predicted outcomes better than the time to return of spontaneous circulation. *Conclusions:* In our single-center cohort utilizing moderate sedation, the bispectral index and suppression ratio recorded after the first dose of intermittent neuromuscular blockade were accurate and very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest.

Keywords Electroencephalography · Therapeutic hypothermia · Heart arrest/complications/*diagnosis/*therapy · Predictive value of tests · Prognosis · Treatment outcome

Introduction

Cardiac arrest is a major cause of death and disability throughout the world. Despite improvements in care, out-of-hospital arrest remains a devastating event, with overall mortality above 90% and persistent cognitive impairment for many survivors [1, 2]. Therapeutic hypothermia (TH) attenuates brain injury and improves survival in comatose survivors of cardiac arrest, yet more than half of these patients still suffer a poor neurological outcome [3–6].

Very early determination of brain injury severity within hours after cardiac arrest would allow clinicians to triage patients to the most appropriate therapeutic interventions. Careful reviews of existing approaches to very early outcome prediction based on cardiac rhythm, duration of anoxia or CPR, and very early neurological findings conclude that these tools cannot reliably

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discriminate between patients with poor versus favorable outcomes [7, 8]. Furthermore, those modalities have not been validated with TH routinely incorporated as part of post-cardiac arrest care [1, 9–13].

Monitoring with electroencephalography (EEG) has been recommended during TH [9, 14], and both human and animal data suggest that EEG and somatosensory-evoked potentials correlate with neurological outcomes [15–21]. EEG and evoked potential testing requires experienced specialists for application and interpretation and is often unavailable [11]. Recent reviews have identified the need for simpler EEG technology that non-neurologists can routinely perform and interpret [1, 10, 22].

The bispectral index (BIS) is a processed EEG monitoring tool that reports the level of consciousness, ranging from zero (equivalent to a fully suppressed isoelectric EEG) to 100 (awake patient) [23, 24]. An accompanying variable, the suppression ratio (SR), estimates the percentage of each 63 s epoch that is isoelectric, also ranging from 0–100%. These processed EEG variables have been used to monitor patients during anesthesia practice and in the ICU. We performed a prospective study to test the hypothesis that very early BIS and SR measurements are predictors of neurological outcome after cardiac arrest.

Materials and methods

This investigation was conducted from July 2005 to January 2009 at Maine Medical Center, a 600-bed tertiary care teaching hospital in Portland, Maine. All patients presenting with hypoxic-ischemic encephalopathy (failure to respond appropriately to verbal commands absent sedating medication) within 12 h of return of spontaneous circulation (ROSC), irrespective of initial cardiac rhythm, were considered for TH. Demographic data including age, gender, initial cardiac arrest rhythm, and estimated time from cardiac arrest to ROSC were recorded from the clinical chart. Details of the sedation and neuromuscular blockade protocols and hypothermia protocol are included as an electronic supplement.

BIS and SR monitoring

The BIS Extend sensor (Aspect Medical Systems, Norwood, MA) was placed by bedside nurses when TH was initiated, monitoring leads FPZ and AT1 or AT2. BIS monitoring continued until rewarming was completed, and sedation was then adjusted to a Sedation-Agitation Scale score of 3–4 [25]. Patients were monitored using the Aspect A-2000 (BIS-XP platform, software version 3.1) or Aspect VISTA monitoring system, which were used interchangeably. Pilot data from our center suggested that TH patients frequently have significantly elevated electromyographic (EMG) activity related to shivering and muscle activity that affects the EEG signal, so we investigated BIS and SR values after the first dose of neuromuscular blockade when muscle artifact was absent. We measured BIS1 and SR1 as the sustained plateau values in the 5–10 min after the first dose of NMB by observing the trend line from the Aspect monitor [26]. BIS and SR values just before NMB were also recorded.

Neurological assessment

Neurological function was assessed frequently during hospitalization and at the time of discharge. The Cerebral Performance Category (CPC) score [7] was recorded for all patients and juried by investigators blinded to BIS1 and SR1 values. Good outcome (GO) was defined as a CPC score of 1 or 2, and poor outcome as a CPC score of 3–5. Occasionally, patients may initially recover good neurological function but later die of non-neurological causes (such as repeat cardiac arrest). Some prior studies have classified these patients based on the best attained neurological status rather than final clinical outcome [15, 27]. Our primary analysis, including receiver-operator characteristic (ROC) curves and regression modeling, scored these patients conservatively, based on CPC at hospital discharge. A secondary analysis reports outcomes based on best attained neurological status.

Statistics

Unless otherwise noted, continuous data are reported as median values (interquartile range 25–75%). Group differences for continuous variables were compared using the Mann–Whitney *U* test and dichotomous variables with the chi-square test (or Fisher exact test if expected cell frequencies were less than 5). To assess the ability of BIS1, SR1, and time to ROSC to predict outcome, ROC curves and area under the curve (AUC) with 95% confidence intervals were calculated using Analyse-It^{TM} software. Optimal cutoff point values to predict good outcome (CPC 1 or 2) and poor outcome (CPC 3–5) for the pre-NMB BIS, BIS1, SR1, and time to ROSC were determined using the maximum Youden index (J = sensitivity + specificity –1) [28].

A logistic regression model was constructed to evaluate the independent predictive ability of BIS1 and SR1 in the presence of other early outcome predictors using SAS software Version 9.1 (*SAS* Institute Inc., Cary, NC). In addition to the BIS1 and SR1, potential early predictor variables included the continuous variable time to ROSC (min) and the dichotomous variables witnessed arrest (vs. not) and initial cardiac rhythm (ventricular tachycardia or

fibrillation vs. other). Because BIS1 and SR1 were almost perfectly correlated ($r = -0.96$), we report the results for BIS1 alone in the model. For all tests, $p < 0.05$ was required for statistical significance.

Results

Ninety-seven intubated, mechanically ventilated patients were treated with TH. Fourteen patients were excluded because they did not complete the full course of hypothermia and rewarming ($n = 4$), never received neuromuscular blockade ($n = 3$), had support withdrawn prior to 72 h precluding neurological evaluation ($n = 6$), or had care adjusted in response to the BIS1 value ($n = 1$). The remaining 83 patients received 18–24 h of hypothermia and were supported for at least 72 h (Table 1). The initial cardiac arrest rhythms included ventricular tachycardia or fibrillation (52), pulseless electrical activity (21), asystole (9), and unknown rhythm (1). The median time from collapse to ROSC was 22 (12–35) min, ranging from 4–68 min. Among the entire study cohort including all ages and rhythms, primary analysis based on discharge status revealed that 40% (33/83) recovered to a good outcome. In a cohort of patients matching HACA inclusion criteria (≤75 years old, only VT or VF as presenting cardiac rhythms, witnessed arrest, and total time prior to ROSC <60 min), 62% (21/34) made a good neurological recovery [4].

Table 1 Clinical characteristics of the patients treated with therapeutic hypothermia

	Total cohort ($n = 83$)
Male *n* (%)	54 (65%)
Age (years)	62.0 (48–72)
Witnessed cardiac arrest, *n* (%)	69 (83%)
VT-VF, *n* (%)	52 (63%)
Time, arrest to ROSC (min)	22 (12–35)
Time, ROSC to BIS1 (min)	280 (176–360)
Temperature at BIS1 (°C)	35.1 (33.2–36.3)
BIS before NMB	84 (76–88)
BIS1	18 (6–36)
SR1	57 (2–86)
D/C Alive, *n* (%)	40 (48%)

Unless otherwise reported, data are presented as median (interquartile range 25–75%)
VT ventricular tachycardia, *VF* ventricular fibrillation, *ROSC* return of spontaneous circulation, *BIS1* BIS plateau value following the first dose of neuromuscular blockade, *NMB* neuromuscular blockade, *SR1* SR plateau value following the first dose of neuromuscular blockade, *D/C* hospital discharge

Table 2 Univariate analysis of factors comparing good and poor outcomes

	Good outcome ($n = 33$)	Poor outcome ($n = 50$)	*P* value
Age (years)	58 (49–71)	66 (48–73)	0.27
Witnessed arrest	31 (94%)	38 (76%)	0.03
VT-VF, *n* (%)	28 (85%)	24 (48%)	0.001
Non-VT-VF, *n* (%)	5 (15%)	25 (50%)	
Time to ROSC (min)	13 (9–22)	28 (18–38)	0.001
BIS before NMB	82 (76–88)	84 (75–89)	0.49
BIS1	37 (28–40)	7 (3–15)	<0.001
SR1	8 (0–31)	83 (66–94)	<0.001

Non-VT-VF includes 5 pulseless electrical activity (PEA) and 0 asystole events in the good outcome group and 16 PEA and 9 asystole events in the poor outcome group. One patient in the poor outcome group had an unknown rhythm
VT ventricular tachycardia, *VF* ventricular fibrillation, *ROSC* return of spontaneous circulation, *BIS* bispectral index, *NMB* neuromuscular blockade, *SR* suppression ratio

BIS1 and SR1 data

The first dose of NMB was administered 84 (45–166) min after initiation of TH, and 280 (176–360) min after ROSC, at a mean bladder temperature of 35.1 (33.2–36.3)°C. As shown in Table 2, the BIS1 was greater in patients with good outcome, and the SR1 less. The time to ROSC was lower among patients with good outcome, and BIS before NMB was not significantly different between groups. None of 37 patients regaining consciousness recalled neuromuscular blockade or the period of hypothermia. There was no correlation between BIS1 and sedative dose ($r = 0.02$) or bladder temperature ($r = 0.09$). Time from ROSC to BIS1 showed a small but not statistically significant correlation with BIS1 ($r = 0.32$).

As shown in Fig. 1a (a 31-h recording during hypothermia and rewarming representative of patients with good outcome), administration of NMB caused a characteristic rapid drop of EMG power from 51 to a baseline of 27 decibels (dB), with a consistent post-NMB plateau value for the BIS1 (40) and rare emergence of SR values less than 10. By comparison, Fig. 1b (a more focused 4-h tracing characteristic of patients with poor outcome) shows more severe reduction in BIS1 (4) and higher SR1 (92) values compared to Fig. 1a.

Prediction of neurological outcome

The ROC curve for BIS1 to predict poor neurological outcome as defined by discharge status is displayed in Fig. 2a. The AUC is 0.91 (95% CI 0.85–0.98, $p < 0.001$), and the cutoff point of BIS1 ≤ 22 predicted a poor outcome with a likelihood ratio (LR) of 14.2 (sensitivity 0.86 and specificity 0.94). Figure 2b shows the ROC curve for SR1, with an AUC of 0.90 (95% CI 0.83–0.98,

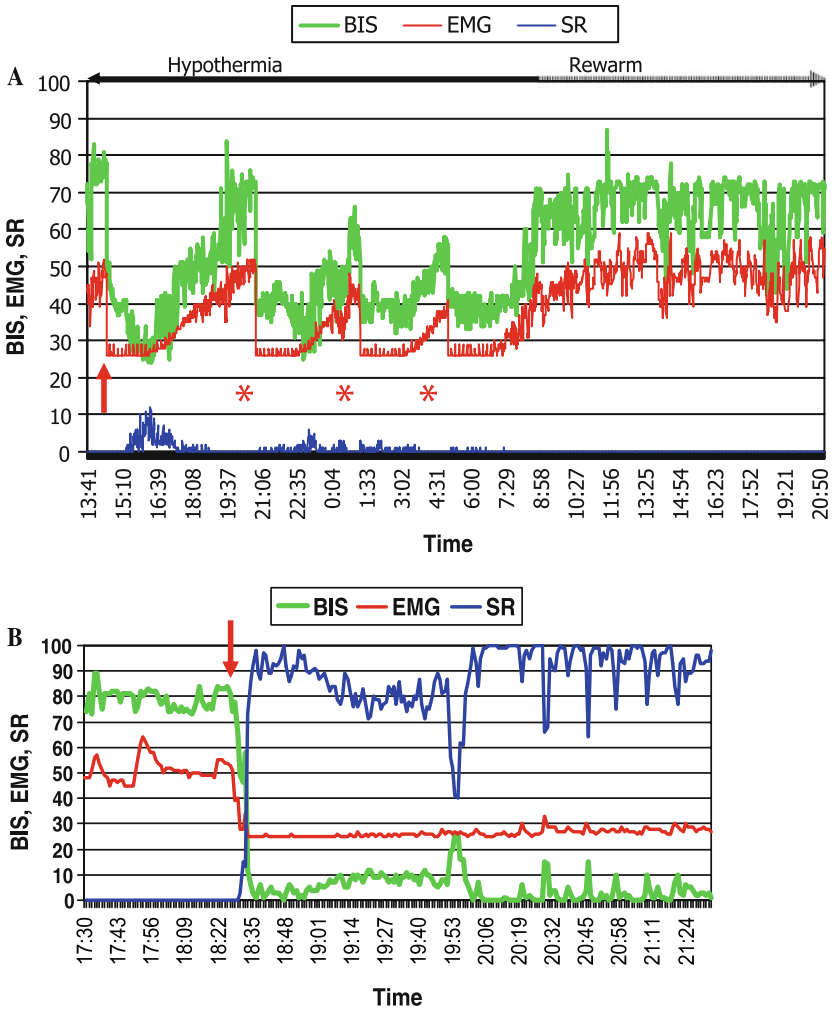

Fig. 1 **a** BIS and SR with a good neurological outcome. BIS (*green line*), EMG (*red line*), and SR (*blue line*) in a 54-year-old man with a VF arrest and a 12-min time to ROSC. Vecuronium was administered at 14:31 (*red arrow*) for shivering, and the BIS fell from 78 to a BIS1 of 40, the EMG from 51 to 27 dB, and the SR1 rose to 9 (visible at the *bottom* of the *graph*). Additional vecuronium was administered three more times (*red asterisks*). The patient ultimately had a good neurological outcome (CPC = 1). **b** BIS and SR with a poor neurological outcome BIS, SR, and EMG in an 84-year-old man with VF arrest and a 22-min time to ROSC. Vecuronium was administered at 18:26 (*red arrow*) for shivering, and the BIS fell from 82 to a BIS1 of 3, the EMG from 53 to 25 dB, and the SR1 rose to 93. The patient eventually had a poor neurological outcome (CPC = 5)

$p < 0.001$). SR1 $\geq$ 48 predicted poor outcome with a LR of 12.7 (sensitivity 0.84 and specificity 0.93).

Figure 3 shows ROC curves for BIS1, time to ROSC, and BIS before NMB to predict poor outcome. Time to ROSC performed less well with an AUC of 0.75 (95% CI 0.63–0.86, $p \leq 0.001$), and the cutoff point $\geq$28 min predicted poor outcome with a LR of 3.8 (sensitivity 0.59 and specificity 0.84). The BIS value before NMB performed poorly, with an AUC of 0.44 (95% CI 0.31–0.58, $p = 0.80$). BIS1 performed significantly better than time to ROSC (AUC difference 0.16, 95% CI 0.05–0.28, $p = 0.006$), as did SR1 (AUC difference 0.16, 95% CI 0.05–0.27, $p = 0.005$).

When predicting good outcome (CPC 1 or 2), BIS1 remained effective with an AUC of 0.91 (0.85–0.98, $p < 0.001$), with a cutoff point value of $\geq$24 yielding a LR of 6.7 (sensitivity 0.94 and specificity 0.86). SR1 showed similar results, with an AUC of 0.90 (0.83–0.98, $p \leq 0.001$), and a cutoff point value of $\leq$46 yielding a LR of 6.0 (sensitivity 0.93, specificity 0.84). Time to ROSC again performed less well than BIS1 or SR1, with an AUC of 0.75 (0.63–0.86), and a cutoff point of $\leq$25 min yielded a LR of 2.0 (sensitivity of 0.84, specificity of 0.59).

Multivariable logistic regression model

BIS1 as a continuous variable predicted poor outcome with an odds ratio (OR) of 1.14 (95% CI 1.09–1.20, $p < 0.001$) per BIS unit, and a *c*-statistic of 0.91. When controlling for witnessed arrest, cardiac rhythm, and time to ROSC, BIS1 remained a significant predictor with an OR of 1.14 (95% CI 1.07–1.20, $p < 0.001$), while cardiac rhythm (VT/VF vs. other rhythms) demonstrated an OR of 0.22 (95% CI 0.04–1.0, $p = 0.06$), and witnessed arrest (95% CI OR = 0.06–7.5) and time to ROSC (95% CI OR = 0.97–1.1) did not predict outcome. The *c*-statistic for this enhanced model was only slightly improved from the model including BIS1 alone ($c = 0.93$). BIS1 as a dichotomous variable ($\leq$22) predicted PO with an OR of 95.2 (95% CI 18–490, $p < 0.001$) and *c*-statistic of 0.90. When controlling for the other variables, BIS1 remained a

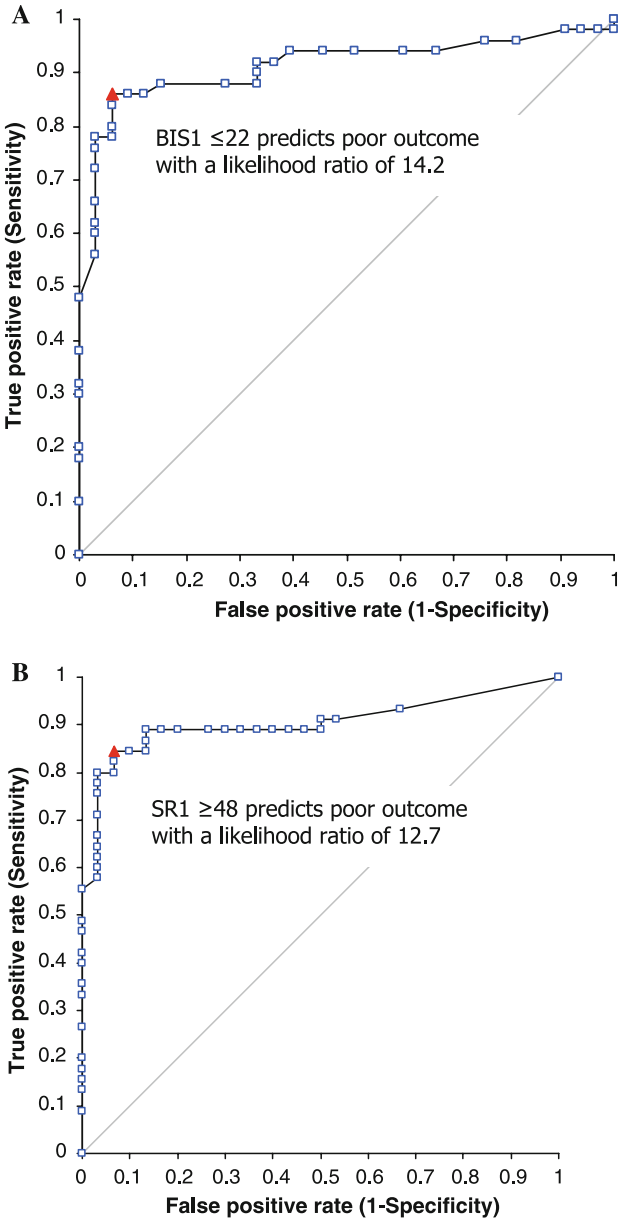

Fig. 2 **a** Receiver-operator characteristic (ROC) curve describing the accuracy of BIS1 to predict poor neurological outcome. The area under the curve (AUC) is 0.91 (95% CI 0.85–0.98, $p < 0.001$). At a cutoff point of BIS1 ≤22 (*red triangle*), the likelihood ratio (LR) of a poor outcome was 14.2 (sensitivity 0.86 and specificity 0.94). **b** ROC curve describing the accuracy of SR1 to predict a poor neurological outcome. The AUC is 0.90 (95% CI 0.83–0.98, $p < 0.001$). At a cutoff point of SR1 ≥48 (*red triangle*), the LR of a good outcome was 12.7 (sensitivity 0.84 and specificity 0.93)

significant predictor with an OR of 110 (95% CI 15–806, $p < 0.001$), while cardiac rhythm had an OR of 0.12 (95% CI 0.02–0.74, $p = 0.02$) and witnessed arrest (95% CI OR = 0.03–11.5) and time to ROSC (95% CI OR = 0.94–1.1) were not independently associated with outcome. The *c*-statistic for this enhanced model was 0.94.

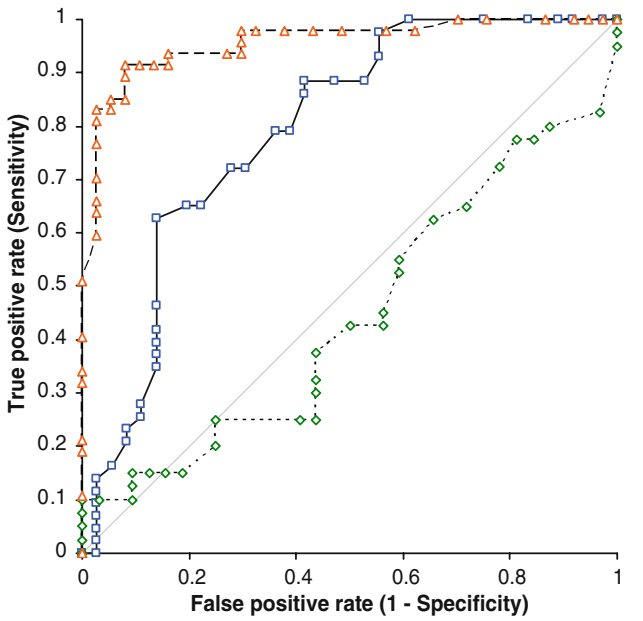

Fig. 3 Comparison of ROC curves to predict poor neurological outcome for BIS1, time to ROSC, and BIS prior to neuromuscular blockade. *Red triangles* refer to BIS1, *blue squares* to "time to ROSC," and *green diamonds* to BIS obtained prior to neuromuscular blockade. BIS1 performed better than time to ROSC (AUC difference 0.16, 95% CI 0.05–0.28, $p = 0.006$)

Table 3 shows the varying percentages of good neurological outcome by BIS decile for the primary analysis definition (discharge status) and the secondary analysis using best neurological outcome during hospital stay. The four subjects who awoke but later died had BIS1 values of 63, 44, 40, and 34. As compared to the primary analysis outcomes, assigning these four patients to the good outcome category changes the predictive power of the three highest BIS deciles to 100% for good outcome.

Discussion

We used a widely available and easily interpreted form of processed, quantitative EEG for very early prediction of neurological outcome after cardiac arrest in patients receiving TH. The BIS1 and SR1 obtained after the first dose of neuromuscular blockade appear to be sensitive and specific predictors of both good and poor neurological outcome in our single-center study. Both BIS1 and SR1 appear to be more accurate predictors of outcome than time from collapse to ROSC, initial cardiac rhythm, and witnessed versus unwitnessed arrest. In addition, a BIS value less than 50 after neuromuscular blockade may be a useful target for titrating sedation to prevent recall of neuromuscular blockade during TH. If confirmed in additional studies, BIS1 and SR1 would be valuable

Table 3 Outcome defined by discharge status and best neurological status for each BIS1 decile

Decile	*N*	BIS1 median (range)	Good outcome[a] (%) (95% CI)	Good outcome (best CPC)[b] (%) (95% CI)
1	9	0 (0–1)	0 (0–34)	
2	7	3 (2–4)	0 (0–40)	
3	8	6 (5–6)	0 (0–37)	
4	10	7.5 (7–13)	10 (0–46)	
5	7	15 (14–17)	14 (1–53)	
6	8	23 (18–26)	38 (13–70)	
7	9	29 (28–32)	78 (44–95)	
8	9	37 (34–38)	89 (54–100)	100 (65–100)
9	8	40 (39–41)	88 (51–100)	100 (63–100)
10	8	44.5 (44–63)	75 (40–94)	100 (63–100)

[a] Good outcome as defined by discharge CPC status

[b] Good outcome as defined by best neurological status during hospital stay, even if discharge status was worse. See text for discussion

additions to allow better prediction of severity of neurological impairment very early after cardiac arrest, and may be one of the first to predict good outcome accurately.

In a recent review, Wijdicks [8] concluded that initial cardiac rhythm and duration of anoxia cannot discriminate accurately between poor and favorable outcomes. Previously, Booth concluded that no very early clinical exam findings accurately predict outcome, and no clinical findings predict good neurological outcome at any time [7]. Other attempts at early outcome prediction after cardiac arrest have utilized serum biomarkers such as neuron-specific enolase or S-100, but these are unreliable within hours after cardiac arrest, achieving greater accuracy over 2–4 days [29–31]. Although the absence of the evoked N20 response to median nerve stimulation seems to be a reliable predictor of poor outcome, especially if performed more than 24 h after restoration of spontaneous circulation, the presence of those waveforms does not predict a good outcome [18, 32]. If BIS1 and SR1 are confirmed to be reliable very early predictors of both good and poor outcome, clinicians may better identify patients at high risk for poor outcome who might benefit from investigational therapies, and also patients likely to make a good recovery who might benefit from early coronary revascularization [33, 34].

Several prior studies have shown agreement between BIS or SR and neurological outcome in unsedated ICU patients [35, 36]. Shibata reported lower BIS values at ICU admission in cardiac arrest survivors with poor neurological outcome [37]. Their cohort had higher BIS values (mean 80) than our reported BIS1, possibly due to our routine application of hypothermia and sedation during neuromuscular blockade. Our SR data suggest that greater EEG suppression (higher SR1) is associated with a worse neurological outcome. This is consistent with Geocadin and colleagues' reports after graded asphyxia in rats [19, 20]. Classification schemes have varied between studies, but the association between EEG suppression and poor outcome has been reported both in humans after cardiac arrest and in general ICU patients [15, 38, 39].

A recent report of BIS measured during prehospital resuscitation concluded that the bispectral index was "useless" after cardiac arrest [40]. The population they described differed from our cohort in that no patient in their study received neuromuscular blockade, and many did not survive the initial resuscitation. BIS values obtained prior to neuromuscular blockade in our cohort were poor predictors of outcome, consistent with those results. We believe that EMG artifact must be minimized with neuromuscular blockade to allow EEG neuroprognostication in cardiac arrest survivors.

Whether BIS1 should be treated as a continuous or dichotomous variable is not certain. Although the BIS1 cutoff point at $\leq$22 has the best Youden index, balancing sensitivity and specificity to predict outcome, this point could be adjusted depending on how the variable was being used. The logistic regression model as a continuous variable suggests that each decrease in BIS1 of 1 point increases the chance of a poor outcome by 14%. Although two patients with BIS1 values of 6 or 20 would both be less than 22 and predicted to have a poor outcome, magnitudes of clinical difference separate those two examples. Additional testing with larger samples is needed to better define these issues.

Our results are preliminary, and several limitations deserve comment. The study was conducted in a single center with a moderate sample size. Validation among patients at other centers with different hypothermia protocols is needed. The impact of time after ROSC and body temperature on the accuracy of BIS1 and SR1 is not known. Our measurements occurred at the time of the first dose of NMB—a median of 280 min after ROSC in this study, rather than at a specified time point after ROSC. Temperature has a minimal effect on the BIS (1 BIS unit decrease per degree Celsius decrease) [41], and other potential confounders such as sedative and analgesic medication doses did not appear to affect prognostication, but these issues deserve further study. We did not routinely monitor patients with continuous EEG, but have since added this to our hypothermia protocol. The incidence of early seizures and what effect they may have on BIS1 and SR1 determinations is also unknown. Future studies should compare BIS1 and SR1 to EEG, neuron-specific enolase, S-100B, evoked potentials, and neurological exam findings obtained very early after cardiac arrest.

We utilize a moderate sedation protocol during hypothermia (see electronic supplement), similar to that described by Bernard and Rundgren [3, 15] rather than the deeper sedation used by Holzer or Oddo [4, 42]. It remains unclear if sedation during TH should be provided primarily for patient comfort and to avoid recall during NMB, or if deeper sedation should be used to suppress

seizures and decrease cerebral metabolic activity. Sedation, neuromuscular blockade, and altered drug metabolism related to hypothermia can confound neuroprognostication after cardiac arrest [1, 43], but the desire to avoid prolonged sedative effects must be balanced by the risk for inadequate sedation during neuromuscular blockade (reported to occur in 18–36% of ICU patients) [44, 45]. By infusing low-dose propofol or intermittent lorazepam titrated to keep the BIS less than 50 after NMB, our patients had no recall of this intervention, similar to prior non-TH BIS studies [46, 47].

Four patients in our cohort initially awoke after hypothermia and demonstrated good neurological function, but later died from repeat cardiac arrest or other medical problems. Although we chose to honor the Utstein consensus by classifying their deaths as poor outcomes despite prior awakening, this approach underestimates the accuracy of tests designed to predict neurological recovery. Future studies might be better designed if such patients are identified as having a good neurological outcome.

Formal prognostication after cardiac arrest should be deliberate, multidisciplinary, and based on validated parameters. Our preliminary data suggest that the bispectral index and suppression ratio, coupled to neuromuscular blockade, may contribute to that assessment, and may be especially valuable very early after cardiac arrest. In addition, the bispectral index may verify adequate sedation during the period of neuromuscular blockade. BIS monitoring is widely available, noninvasive, and easily applied and interpreted by clinicians. Our data suggest it may also predict neurological outcome after cardiac arrest, but additional research in larger cohorts and different centers is warranted to confirm these findings.

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