CrossMark

Quantitative measures of EEG for prediction of outcome in cardiac arrest subjects treated with hypothermia: a literature review

Shadnaz Asgari[1,2] · Hana Moshirvaziri[1] · Fabien Scalzo[3,4] · Nima Ramezan-Arab[4,5]

Abstract

Cardiac arrest (CA) is the leading cause of death and disability in the United States. Early and accurate prediction of CA outcome can help clinicians and families to make a better-informed decision for the patient's healthcare. Studies have shown that electroencephalography (EEG) may assist in early prognosis of CA outcome. However, visual EEG interpretation is subjective, labor-intensive, and requires interpretation by a medical expert, i.e., neurophysiologists. These limiting factors may hinder the applicability of such testing as the prognostic method in clinical settings. Automatic EEG pattern recognition using quantitative measures can make the EEG analysis more objective and less time consuming. It also allows to detect and display hidden patterns that may be useful for the prognosis over longer time periods of monitoring. Given these potential benefits, there have been an increasing interest over the last few years in the development and employment of EEG quantitative measures to predict CA outcome. This paper extensively reviews the definition and efficacy of various measures that have been employed for the prediction of outcome in CA subjects undergoing hypothermia (a neuroprotection method that has become a standard of care to improve the functional recovery of CA patients after resuscitation). The review details the State-of-the-Art and provides some perspectives on what seems to be promising for the early and accurate prognostication of CA outcome using the quantitative measures of EEG.

1 Introduction

Cardiac arrest (CA) is the leading cause of death in the United States [1, 2]. Each year, about 325,000 people have an out-of-hospital cardiac arrest, whereas only 10–20% of them survive [3, 4]. Poor functional outcomes such as moderate to severe disability or persistent vegetative state

✉ Shadnaz Asgari
Shadnaz.Asgari@csulb.edu

1 Biomedical Engineering Department, California State University, Long Beach, 1250 Bellflower Blvd.-MS 8302, Long Beach 90840-8302, CA, USA

2 Computer Engineering and Computer Science Department, California State University, Long Beach, CA, USA

3 Department of Computer Science, University of California, Los Angeles, CA, USA

4 Department of Neurology, University of California, Los Angeles, CA, USA

5 Neuroscience and Stroke program, Long Beach Memorial Medical Center, Long Beach, CA, USA

are common among the survivors [5, 6]. Early and accurate prediction of CA outcome is of tremendous value both in terms of (a) optimizing the clinical treatment/intervention, and (b) health care cost management. The accurate prognosis of CA would also help families of the patients to make a better-informed decision with respect to potential life support withdrawal versus continued supportive care [7]. In addition to higher survival rate and better functional outcome, therapeutic hypothermia (TH) has been associated with shorter hospital stay duration for CA patients [8, 9]. Thus, TH has recently become a standard of care after resuscitation [9]. However, CA outcome prognostication for the patients treated with TH is currently qualitative and poorly understood [7, 10]. This is mainly due to the use of sedative and paralytic agents, and neuroprotective effects of hypothermia that reduce sensitivity of the conventional CA prognostication markers and/or change their optimal timing for the outcome prediction [7, 9, 11–15].

Recent studies have shown that electroencephalography (EEG) can be useful in CA outcome prediction [9]. For example, several EEG patterns (including the absence

of EEG reactivity, the presence of burst suppression with generalized epileptiform activity, and the presence of generalized periodic complexes on a flat background) have been associated with poor outcome [16, 17]. In contrast to other prognostication modalities, EEG measurement can be performed easily, continuously and noninvasively at the patient's bedside. But visual EEG pattern recognition is laborious and subjective [18]. It also requires a specialized training in EEG interpretation and many nurses and physicians in intensive care units (ICUs) lack such expertise [19]. Recent advances in the quantitative EEG analysis can overcome the above limitations [7, 20, 21]. As a result, over the last few years, there have been a growing interest in the development and employment of quantitative measures of EEG to predict CA outcome [22–28]. The aim of this review is to discuss the State-of-the-Art in employment of quantitative measures of EEG for prediction of the outcome in CA subjects treated with hypothermia. The review can provide a platform for the future potential development and examine of new measures and/or methods for the early and accurate CA outcome prediction for the patients undergoing hypothermia.

2 Materials and methods

Pubmed database was searched for the articles which were published between year 2000 and the present time (August 2017) using (logical conjunction of) the following keywords: "quantitative EEG" and "cardiac arrest" and "hypothermia". In our review, we considered both animal and human studies. The previous investigations on the effect of changes in temperature of the brain have indicated that hypothermia has relatively similar influences on EEG in animals and humans [29]. The search resulted in more than 40 publications. The abstracts of these publications (and the body of the papers if the abstracts did not provide sufficient information) were studied to verify the relevancy of each paper to the subject of our search (employing quantitative measures of EEG for automatic CA outcome prediction in subjects undergoing hypothermia). Following exclusion of the irrelevant publications, remaining papers were read carefully, their proposed measures were identified and their results were summarized.

3 Results

Exclusion of the irrelevant papers (those not related to employment of quantitative measures of EEG, or not related to cardiac arrest or hypothermia) resulted in selection of 24 papers. Table 1 lists the selected papers along with a summary of the main findings of the papers. Table 2 includes a list of quantitative measures (features) of EEG which have been employed in prediction of CA outcome for the subjects

undergoing hypothermia. For simplicity, the identified measures were grouped into four groups: conventional entropy-based measures; burst suppression measures; information quantity measures; and combined measures. In the following subsections, we go over the definition of each measure and discuss its efficacy in prognostication of CA outcome for hypothermia subjects.

3.1 Conventional entropy-based measures

In information theory, Shannon entropy is defined as a measure of the uncertainty in a random variable X by quantifying the expected value of the information contained in a signal [30]. Entropy is typically measured in bits as

$$Shannon\ Entropy = -\sum_{i}^{N} p_i \log_2 p_i, \tag{1}$$

where p_i is the probability of random variable X being equal to value X_i for $i = 1, 2, ..., N$. Note that $\sum_{i=1}^{N} p_i = 1$. A higher level of randomness or complexity in the data generally indicates larger entropy values.

Similar to many other organs, brain can be considered as a system with high level of complexity (entropy). A reduction of biological system's complexity is often interpreted as a pathological or deteriorating state [31]. Brain injury and the disruption of its normal functionality can result in the reduction of brain's complexity [32]. Therefore, using an appropriate EEG entropy analysis, one may be able to track the brain's recovery progress after brain injury. Several conventional entropy-based measures have been proposed for the CA outcome prediction. Here, we review the definition of those which have shown efficacy in prediction of the outcome when the subject went under hypothermia treatment.

3.1.1 Spectrum entropy

The spectrum entropy (*SE*) of the EEG signal is calculated as the Shannon entropy of the normalized energy of the signal within certain frequency subbands of interest. In other words, the probability p_i in Eq. (1) is defined as

$$p^i = \frac{E_i}{\sum_{i=1}^{N} E_i}, \tag{2}$$

where E_i is the energy of the signal within ith subband calculated from power spectral analysis of the EEG signal.

Chen et al. choose $N = 4$ frequency subbands to study the efficacy of *SE* as a prognostic measure of CA outcome in rats: Delta (0.5–4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz), and Beta (13–30 Hz) [33]. The results of this study indicated that the hypothermic rats have significantly higher values

Table 1 List of selected publications along with a summary of their results (ordered based on the year of publication)

Paper	Year	Subjects	EEG feature	How EEG feature was obtained?	Summary of results
Jia et al. [25]	2006	28 rats	Information quantity (IQ)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its feature was extracted with in-house software	The 72-h NDS of the hypothermia group was significantly improved compared to the normothermia. The IQ showed significantly different values between hypothermia and normothermia groups. There was a trend toward minor metabolic acidosis in the normothermic controls compared to hypothermic rats with a slight but statistically significant difference in bicarbonate concentration at 40 min post-CA
Shin et al. [49]	2006	30 rodents	Information quantity (IQ)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its feature was extracted with in-house software	The IQ was greater for hypothermic than normothermic rats, with a difference of more than 0.2
Jia et al. [19]	2008	28 male Wistar rats	Information quantity (IQ)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its feature was extracted with in-house software	Greater recovery of the IQ was found in rats treated with hypothermia, compared to normothermia and hyperthermia. IQ values correlated strongly with 72-h NDS as early as 30 min post-CA (correlation = 0.735)
Lu et al. [44]	2008	12 Wistar rats	C0 Complexity	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its feature was extracted with in-house software	Significantly greater C0 complexity was found in hypothermic group than that in normothermic group as early as 4-h after the ROSC. C0 complexity at 4-h correlated well with the 72-h NDS (correlation = 0.882)
Shin et al. [50]	2008	13 rats	Subband information quantity (SIQ), and information quantity (IQ)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its features were extracted with in-house software	During hypothermia, SIQ was more correlated with neurological outcome than IQ (correlation of 0.74 vs. 0.65)
Jia et al. [51]	2008	36 rats	Subband information quantity (SIQ)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its feature was extracted with in-house software	The 72-h NDS of the immediate hypothermia (IH, immediately post-resuscitation maintained for 6-h) group was significantly better than the conventional hypothermia (CH, starting 1 h post-resuscitation, maintained 12 h) group. The SIQ values of the IH group was significantly higher. The neuronal cortical activity (measured by Cresyl violet staining) of the IH group was significantly lower. PCO_2 was significantly lower and blood pressure was significantly in IH at 40 min post-CA

Table 1 (continued)

Paper	Year	Subjects	EEG feature	How EEG feature was obtained?	Summary of results
Kang et al. [26]	2009	10 Wistar rats	Multi-scale entropy (MSE)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its feature was extracted with in-house software	Alpha-rhythm MSE measured within 1–2.5-h post-CA was significantly different between the hypothermic and normothermic groups
Wennervirta et al. [21]	2009	30 comatose patients	Burst suppression ratio (BSR), Wavelet subband entropy (WSE), response entropy and state entropy	EEG was measured using (Datex-Ohmeda S/5, GE Healthcare, Helsinki, Finland). Wavelet subband entropy (WSE) was extracted by in-house software. Burst suppression ratio (BSR), response entropy and state entropy were obtained by Datex-Ohmeda entropy module	In the patients with good outcome (CPC of 1 and 2), BSR, WSE, response entropy and state entropy were all significantly higher. However, neuron-specific enolase, protein 100B, and pulsatility index of cerebral blood flow velocity were significantly lower in patients with good outcomes
Leary et al. [61]	2010	62 patients	Bispectral Index (BIS)	BIS monitoring (Aspect Medical Systems, Norwood, MA, USA)	BIS was significantly higher in the good outcome group. BIS at 24 h post-CA was the best predictive of CPC 1–2 outcome compared to the other time points; a BIS cut-point of 45 exhibited a sensitivity of 63% and a specificity of 86%, with a positive likelihood ratio of 4.67
Seder et al. [60]	2010	97 patients	Bispectral Index (BIS)	BIS monitoring (Aspect Medical Systems, Norwood, MA, USA)	The BIS was higher in patients with good outcome (37 [28–40] vs. 7 [3–15]). BIS <22 predicted poor outcome with a likelihood ratio of 14.2 and accuracy of 0.91
Chen et al. [33]	2013	20 male Sprague–Dawley rats	Burst suppression frequency (BSF), and spectrum entropy (SE)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and features were extracted with in-house software	96-h NDS and survival were significantly better in the hypothermic group. BSF and SE were greatly improved in the hypothermic group and correlated with 96-h NDS and survival
Stammet et al. [64]	2013	75 patients	Bispectral Index (BIS)	Quatro sensor from ASPECT Medical Systems Inc., Newton, MA, USA	NSE and S100B levels were significantly lower and BIS values were significantly higher in patients with good outcome (CPC 1–2). Patients with S100b level above 0.03 mg/l and BIS below 5.5 had a 3.6-fold higher risk of poor neurological outcome. S100b and BIS predicted 6-month mortality (log-rank statistic: 50.41)
Riker et al. [62]	2013	509 patients	Bispectral Index (BIS)	models A2000 and VISTA from Covidien Medical, Boston, MA, USA	Patients who awakened early had higher BIS values after the first dose of neuro-muscular blockade

Table 1 (continued)

Paper	Year	Subjects	EEG feature	How EEG feature was obtained?	Summary of results
Tjepkema et al. [54]	2013	109 patients	Cerebral Recovery Index (CRI)	EEG was measured using Neurocenter (Clinical Science Systems, Voorschoten, The Netherlands) and its feature was extracted with in-house software	CRI at 24-h post-CA classified the good outcome (CPC 1–2) versus poor outcome (CPC > 2) with specificity of 100%
Selig et al. [63]	2014	79 patients	Bispectral Index (BIS)	A-2000 system XP, software version 3.30, Aspect Medical Systems Company, Newton, Massachusetts, USA and the BIS-Quattro sensor electrodes	Using BIS < 40 as threshold criteria, poor neurological outcome was predicted with a specificity of 89.5% and a sensitivity of 85.7%. The odds ratio for predicting a poor outcome was 0.921 (95% CI 0.853–0.985)
Noirhomme et al. [28]	2014	46 comatose patients	Burst Suppression Ratio (BSR) and Approximate Entropy (AE)	EEG was measured using Viasys Neurocare, Madison, WI and its feature was extracted with in-house software	BSR was significantly lower and AE was significantly higher in patients with good outcome (CPC 1–2)
Ghassemi et al. [10]	2014	167 patients	Cerebral Recovery Index (CRI), and Enhanced Cerebral Recovery Index (ECRI)	EEG was measured with standard 10–20 montage (no further info is provided) and its features were extracted with in-house software	Relative to CRI, ECRI measured in 24-h post-CA increased the classification accuracy of good outcome (CPC 1–2) versus poor outcome classification by an average of 27%
Seder et al. [48]	2014	171 patients	Bispectral Index (BIS)	models A2000 and VISTA from Covidien Medical, Boston, MA, USA	BISi < 10 suffered 82% neurological-cause and 91% overall mortality, BISi 10–20 suffered 35% neurological and 55% overall mortality, and BISi > 20 suffered 12% neurological and 36% overall mortality
Stammet et al. [65]	2014	75 patients	Bispectral Index (BIS)	Quatro sensor from ASPECT Medical Systems Inc., Newton, MA, USA	BIS was significantly higher in good outcome (CPC 1–2). Analysis of BIS recorded every 30 min provided an optimal prediction after 12.5 h, with an accuracy of 0.89
Deng et al. [52]	2015	14 rats	Subband information quantity (SIQ), and information quantity (IQ)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and features were extracted with in-house software	Both IQ and SIQ at as early as 1-h post-CA had high correlation (0.8) with 72-h NDS score. IQ could identify the presence of high-frequency oscillations during the recovery from severe brain injury
Deng et al. [53]	2015	24 Wistar rats	Subband information quantity (SIQ)	EEG was measured using DI700 Windaq (Data Q Instruments, Akron, OH), and its features was extracted with in-house software	The Gamma-band SIQ had the strongest correlation (between 0.52 and 0.78), while Delta-band SIQ had the lowest correlation to 72-h NDS score Better recovery of Gamma-band SIQ was found in the hypothermia group compared with the normothermia group and hyperthermia group

Table 1 (continued)

Paper	Year	Subjects	EEG feature	How EEG feature was obtained?	Summary of results
Moshirvaziri et al. [18]	2016	11 comatose patients	Wavelet subband entropy (WSE)	EEG was measured using Viasys Neurocare, (Madison, WI) and its feature was extracted with in-house software	WSE over the frequency range of 64–100 Hz captured from the inferior frontal lobes were significantly higher in those survived
Jouffroy et all [66]	2017	46 patients	Bispectral Index (BIS)	(BIS monitor – Covidien©) No further info is provided	BIS values were significantly lower in those who died (4 versus 34)
Ochiai et al. [67]	2017	103 patients	Bispectral Index (BIS)	A-2000 and BISx monitors for different years both from Aspect Medical Systems, MA, USA	Low mean BIS value best predicted poor outcomes with CPC of 3 to 5 with an accuracy of 0.861

of *SE* (and better neurological outcome) relative to normothermic controls. Using a logistic regression analysis, the authors also showed that *SE* value at 6-h after restoration of spontaneous circulation (ROSC) was an independent predictor of 96-h survival outcome in hypothermic group.

Two spectrum entropy-based variables that can be measured using a commercially available product (Datex-Ohmeda entropy module, GE Healthcare, Helsinki, Finland) are response entropy and state entropy [22]. State entropy is the entropy of the normalized energy of the signal over the EEG-dominant frequency range of 0.8–32 Hz, indicating the effect of hypnotics on the cortex. On the other hand, response entropy is the spectrum entropy over the frequency range of 0.8–47 Hz (including EEG and facial electromyography frequency components) and can be used to detect the patient's responsiveness [21, 22]. In a study of 30 comatose patients by Wennervirta et al., both relative entropy and state entropy demonstrated significantly higher values during the first 24 h after CA in patients with cerebral performance category (CPC) [34] of 1 or 2 comparing to the other patients [21].

3.1.2 Approximate entropy

Approximate entropy (*ApEn*) is a parameter that quantifies the unpredictability of fluctuations in a time series [35]. Since its introduction two decades ago, *ApEn* has been widely used to characterize the complexity of various biological and physiological data [36]. *ApEn* is defined as the negative natural logarithm of the probability that the data sequences within a time series that are close for m points remain close for an additional point ($m + 1$ points).

For an EEG signal $\{s(i) \mid i = 1, 2, ..., N\}$, one can define a template vector $\mathbf{X}_m(i)$ as

$$\mathbf{X}_m(i) = \{s(i + k) | 0 \leq k \leq m - 1\}. \tag{3}$$

Note that there exist $N - m + 1$ of such vectors where $1 \leq i \leq N - m + 1$. Now, let us assume that the distance between two vectors $\mathbf{X}_m(i)$ and $\mathbf{X}_m(j)$ is the maximum difference of their corresponding scalar components:

$$d(\mathbf{X}_m(i), \mathbf{X}_m(j)) = \max(|s(i + k) - s(j + k)|), \tag{4}$$

where $0 \leq k \leq m - 1$. Vector $\mathbf{X}_m(j)$ with $1 \leq j \leq N - m + 1$ is called a match for template $\mathbf{X}_m(i)$, if $\mathbf{X}_m(j)$ is less than r distance away from $\mathbf{X}_m(i)$, i.e., when $d(\mathbf{X}_m(i), \mathbf{X}_m(j)) < r$.

Thus, the probability that vector $\mathbf{X}_m(j)$ is within r distance of $\mathbf{X}_m(i)$ can be calculated as

$$C_i^m(r) = \frac{n_{im}(r)}{N - m + 1}, \tag{5}$$

where $n_{im}(r)$ is the number of matches for template $\mathbf{X}_m(i)$. By averaging all $C_i^m(r)$ as

Table 2 Summary of the State-of-the-Art in employment of quantitative EEG measures (features) for prognostication of outcome in the cardiac arrest subjects treated with hypothermia

Feature group	Feature's name	Feature's efficacy in cardiac arrest prognostication
Conventional entropy-based measures	Spectrum entropy (SE)	●In a study of 20 rats, SE at 6-h post-ROSC was predictive of 96-h survival outcomes [33]
	Approximate entropy (ApEn)	●In a study of 46 comatose patients, the average ApEn was significantly higher in patients with good outcome (CPC 1–2) evaluated at 3-month post-CA [28]
	Multiscale entropy (MSE)	●In a study of 10 rats, alpha-rhythm MSE measured within 1–2.5-h post-CA was significantly different between the hypothermic and normothermic groups. Good recovery outcomes (NDS > 60) was always achieved if the ratio of alpha-rhythm MSE measured at 3-h post-CA to that of the baseline (before-CA) was above 0.85 [26]
	Wavelet subband entropy (WSE)	●In a study of 30 comatose patients, Beta WSE measured between 24 and 48 h post-CA was significantly higher in the good outcome group (CPC of 1–2) evaluated within a 6-month follow-up period [21] ●In a study of 11 comatose patients, 64–100 Hz WSE captured from the inferior frontal lobes were significantly higher in those survived [18]
	C0 Complexity	●In a study of 12 rats, C0 complexity measured as early as 4-h after the ROSC was significantly higher in hypothermic group than normothermic group. In fact, C0 complexity at 4-h correlated well with the 72-h NDS (correlation = 0.882) [44]
Burst suppression measures	Burst suppression ratio (BSR)	●In a study of 46 comatose patients, the average BSR was significantly lower in patients with good outcome (CPC 1–2) evaluated at 3-month post-CA [28] ●In a study of 30 comatose patients, BSR during the first 48 h post-CA was significantly lower in the good outcome group (CPC of 1–2) evaluated within a 6-month follow-up period [21]
	Burst suppression frequency (BSF)	●In a study of 20 rats, BSF at 2-h post-ROSC was predictive of 96-h survival outcomes [33]
Information quantity measures	Information quantity (IQ)	●In a study of 28 rats, the 72-h NDS of the hypothermia group was significantly improved compared to the normothermia. The IQ also showed significantly different values between hypothermia and normothermia groups [25] ●A study of 30 rodents showed that brain injury results in a reduction of IQ, and the average IQ of hypothermic rats was significantly higher than the normothermic rats for various injury levels [49] ●In a study of 28 rats, IQ at 30-min post-CA had strong correlation of 0.735 with 72-h NDS scores [19]
	Subband information quantity (SIQ)	●In a study of 36 rats, SIQ values was significantly higher when hypothermia was administered immediately post-resuscitation and maintained for 6-h relative to when hypothermia started 1 h post-resuscitation and maintained 12 h [51] ●In a study of 13 rats, SIQ showed a higher correlation (0.74) with 72-h NDS scores than IQ (0.65) [50] ●In a study of 14 rats, both IQ and SIQ at as early as 1-h post-CA had high correlation (0.8) with 72-h NDS score [52] ●In a study of 27 rats, the Gamma-band SIQ had the strongest correlation (between 0.52 and 0.78), while Delta-band SIQ had the lowest correlation to 72-h NDS score [53]
Combined measures	Cerebral Recovery Index (CRI) (combination of 5 features) Power, shannon entropy, alpha to delta ratio, regularity, coherence	●In a study of 109 comatose patients, CRI at 24-h post-CA classified the good outcome (CPC 1–2) versus poor outcome (CPC > 2) [54] ●CRI < 0.29 predicted poor outcomes (sensitivity = 55%, specificity = 100%) ●CRI > 0.69 predicted good outcomes (sensitivity = 25%, specificity = 100%)
	Enhanced Cerebral Recovery Index (ECRI) (combination of 9 features) Power, shannon entropy, alpha to delta ratio, regularity, coherence, tsalis entropy area, cepstrum coefficients, Maximum Phase Lag Index, binary low voltage measure	●In a study of 167 comatose patients, ECRI measured in 24-h post-CA increased the classification accuracy of good outcome (CPC 1–2) versus poor outcome classification by an average of 27% [10]

Table 2 (continued)

Feature group	Feature's name	Feature's efficacy in cardiac arrest prognostication
	Bispectral Index (BIS)	• In a study of 62 patients, BIS was significantly higher in the good outcome group. BIS at 24 h post-CA was the best predictive of CPC 1–2 outcome compared to the other time points; a BIS cut-point of 45 exhibited a sensitivity of 63% and a specificity of 86%, with a positive likelihood ratio of 4.67 [61]
		• In a study of 97 patients, BIS was higher in patients with good outcome (37 [28–40] vs. 7 [3–15]). BIS < 22 predicted poor outcome with a likelihood ratio of 14.2 and accuracy of 0.91 [60]
		• In a study of 75 patients, BIS values were significantly higher in patients with good outcome (CPC 1–2). Patients with S100b level above 0.03 mg/l and BIS below 5.5 had a 3.6-fold higher risk of poor neurological outcome [64]
		• In study of 75 patients, using BIS < 40 as threshold criteria, poor neurological outcome(CPC 3–5) was predicted with a specificity of 89.5% and a sensitivity of 85.7% [63]
		• In a study of 509 patients, those who awakened early had significantly higher BIS values after the first dose of neuromuscular blockade [62]
		• In a study of 171 patients, BISi < 10 suffered 82% neurological-cause and 91% overall mortality, BISi 10–20 suffered 35% neurological and 55% overall mortality, and BISi > 20 suffered 12% neurological and 36% overall mortality [48]
		• In a study of 75 patients, BIS was significantly higher in good outcome (CPC 1–2). Analysis of BIS recorded every 30 min provided an optimal prediction after 12.5 h, with an accuracy of 0.89 [65]
		• In a study of 46 patients, BIS values were significantly lower in those who died (4 versus 34) [66]
		• In a study of 103 patients, Low mean BIS value best predicted poor outcomes with CPC of 3 to 5 with an accuracy of 0.861 [67]

$$C_m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} C_i^m(r), \tag{6}$$

we can calculate *ApEn* for EEG signal of finite length *N*, with pattern length *m* and similarity criterion *r*, as

$$ApEn = \log_e \frac{C_m(r)}{C_{m+1}(r)}. \tag{7}$$

Noirhomme et al. employed *ApEn* measure with $m = 2$, $r = 1.4$, and 8-s epochs to study the prognostic value of this parameter in 46 comatose patients in hypothermia [28]. The results revealed that the average *ApEn* value measures during hypothermia was significantly higher in patients with good outcome whose CPC values are 1 or 2.

3.1.3 Multiple scale entropy

A signal complexity is in general a "meaningful structural richness" [37] that incorporates correlations over multiple spatiotemporal scales [38]. While the previously discussed measures of entropy quantify the regularity of time series on a single scale, multiple scale entropy (*MSE*) considers the complexity of the signal over multiple scales. Given the clinical significance of various frequency subbands in EEG analysis, *MSE* may be a more appropriate measure for CA outcome prediction.

For an EEG signal $\{s(i) \mid i = 1, 2, ..., N\}$, *MSE* of the signal is calculated in two steps: For a given scale (λ), first a moving-average filtering (with zero percent overlapping) is applied to the data to obtain a "coarse grained" signal y_j^λ as

$$y_j^\lambda = \frac{1}{\lambda} \sum_{i=(j-1)\lambda+1}^{j\lambda} s(i), \tag{8}$$

where $1 \leq j < \frac{N}{\lambda}$. Then, the sample entropy (a refined version of *ApEn* which excludes self-matching to reduce the estimator's bias [39]) of each coarse-grained signal is calculated. The final *MSE* is obtained as a plot of the calculated sample entropies over a range of potential scale values $\lambda = 1, 2, ...,$.

As synchronous activity in thalamic pacemaker cells are related to the α-rhythm [40], Kang et al. hypothesized that the complexity changes of EEG α-rhythms (measured by α-rhythm *MSE*) may reveal different degrees of brain recovery during hypothermia after CA [26]. Given the sampling frequency of the signal, the scaling factors corresponding to the Alpha band (8–12 Hz) were identified and the values of *MSE* over those scales were averaged and used as the α-rhythm *MSE* measure. The results of this study on rodents showed that α-rhythm *MSE* measure within 1–2.5 h post-CA was significantly different between the hypothermic and normothermic groups. Furthermore, the authors found that good recovery outcomes were always achieved, when the ratio of α-rhythm *MSE* measured at 3-h post-CA to that of the

baseline (before-CA) was above 0.85. In that study, the good outcome was defined as a case where the neurological deficit scale (NDS) was above 60. Note that NDS is an neurological outcome evaluation standard which includes sub-scores of general behavioral deficit, brain-stem function, motor and sensory assessment, behavior, and seizures [41, 42].

3.1.4 Wavelet subband entropy

Discrete Wavelet transform is one of the most efficient tools for the denoising of the transients, non-stationary and aperiodic signals such as EEG with low redundancy and computational complexity.

To calculate Wavelet subband entropy (*WSE*), one needs to first apply a *L*-level discrete wavelet transform to the signal. The value of *L* is usually determined based on the sampling frequency and the clinical subbands of interests. Let us assume that $\mathfrak{I}_i^l$ is *i* th wavelet coefficient at level *l*, where $l = 1, 2, ..., L$. Then, the *l*-level *WSE* can be obtained as the Shannon energy of the squared and normalized version of the coefficients at that decomposition level. In other words,

$$WSE^l = -\sum_{i=1}^{N} p_i^l \log_2 p_i^l \text{ where } p_i^l = \frac{(\mathfrak{I}_i^l)^2}{\sum_{i=1}^{N} (\mathfrak{I}_i^l)^2}. \tag{9}$$

Wennervita et al. employed *WSE* calculated over Beta subband (16–32 Hz) using Daubechies 3 mother wavelet to study the CA outcome for the patients undergoing hypothermia [21]. Their result indicated that Wavelet Beta subband entropy measured between 24 and 48 h post-CA was significantly higher in the good outcome group (CPC of 1–2) evaluated within a 6-month follow-up period.

In a recent study, our group analyzed a dataset of 16-channel EEG signals collected from 11 CA patients undergoing hypothermia at Long Beach Memorial Medical Center using *WSE* [18]. Our results revealed that the frequency oscillations between 64 and 100 Hz captured from the inferior frontal lobes are significantly more complex in the CA patients who survived.

3.1.5 C0 complexity

Another robust measure of the signal's complexity is C0, a percentage of stochastic components of the signal [43]. For an EEG signal $\{s(i) \mid i = 1, 2, ..., N\}$, C0 complexity is defined as

$$C0 = \frac{\sum_{i=1}^{N} |s(i) - y(i)|^2}{\sum_{i=1}^{N} |s(i)|^2} \tag{10}$$

where $\{y(i) \mid i = 1, 2, ..., N\}$ is obtained from EEG signal by zeroing the signal at all frequency components where the power of the signal is lower than the signal's average power. Lu et al. employed C0 complexity to analyze the nonlinear characteristic of EEG for prediction of the outcome in 12 Wistar rats who were randomly undergoing hypothermia and normothermia [44]. Significantly higher C0 complexity values were found in hypothermic group (relative to normothermic group) as early as 4 h after the ROSC. Furthermore, C0 complexity at 4-h post-ROSC was strongly correlated with the 72-h NDS (correlation = 0.882).

3.2 Burst suppression measures

Burst suppression is characterized by the presence of periods of bursting, when EEG amplitude rises above certain threshold typically in the range of 75–250 µV, followed by long periods (at least 0.5 s) of suppression, when EEG shows low amplitude activities (typically below 10 µV) [<l45, 46]. A clear description of an algorithm to automatically detect the burst suppression patterns in EEG signal has been provided by Sarkela et al. in [47]. Several burst suppression features can be used to quantify the EEG background activities, e.g., burst suppression ratio (BSR), and burst suppression frequency (BSF).

3.2.1 Burst suppression ratio

BSR is defined as the ratio between the total suppression time and total recording time [28]. There are commercially available products that can be used to obtain BSR values. Datex-Ohmeda entropy module (from GE Healthcare, Helsinki, Finland) calculates BSR using the algorithm described in [22] for every 1 min of data, while Bispectral Index (BIS) monitors (from ASPECT medical systems Inc., MA, U.S.A) obtains BSR for every 63 s of data using a proprietary algorithm [48].

A study on 30 comatose CA patients treated with induced hypothermia revealed that BSR (measured by Datex-Ohmeda entropy module) during the first 48 h after CA was significantly lower in patients with good outcomes (CPC of 1–2) evaluated within a 6-month follow-up period [21]. Similarly, in another study on 46 CA patients, low BSR values (computed with a software developed in house) were associated with good neurological outcome (CPC of 1–2) evaluated at 3-month post-CA [28].

3.2.2 Burst suppression frequency

BSF is a measure of frequency content of bursts (during burst suppression periods), and can be easily obtained using spectral analysis [33]. Chen et al. found that BSF was significantly

higher in hypothermic rats compared to the control groups. The observed continuous increasing trend of BSF during the first 2 h after resuscitation of rats treated with hypothermia showed the effectiveness of therapeutic hypothermia in brain recovery. This study also indicated that the 2-h post-ROSC BSF value was independently predictive of 96-h survival outcome.

3.3 Information quantity measures

3.3.1 Information quantity

Information Quantity (*IQ*) measure was developed based on the assumption that a better neurotological outcome is associated with larger information content of the brain rhythm [49]. *IQ* is defined as time dependent Shannon entropy of decorrelated EEG signals using discrete wavelet transform (DWT). A sliding temporal window $W(n, w, \Delta)$ is applied to the EEG signal $\{s(i) \mid i = 1, 2, ..., N\}$ such that

$$W(n, w, \Delta) = \{s(i) | i = 1 + n\Delta, ..., 1 + w\Delta\} \quad (11)$$

where w is the length of sliding window, Δ is the sliding step, and $n = 0, 1, ..., \frac{N}{\Delta} - w + 1$. Then using a r-level DWT, the signal within each window is decomposed into frequency subbands that represent standard clinical bands of interest. The DWT coefficients of each window, $WC(r, n, w, \Delta)$, are obtained and the time dependent *IQ* is calculated as

$$IQ(n) = -\sum_{m=1}^{M} p_m(n)\log_2(p_m(n)), \quad (12)$$

where $p_m(n)$ is the probability that the sampled signal belongs to the interval $\{I_m : m = 1, 2, ..., M\}$ and is obtained as the ratio between the number of the samples found within interval I_m and the total number of samples in $WC(r, n, w, \Delta)$.

IQ has demonstrated a superior tracking capability for both frequency changes and dynamic amplitude changes comparing to conventional entropy-based measures such as Shannon entropy and Wavelet entropy.

In a study of 28 rats, the *IQ* values showed significantly difference between hypothermia and normothermia groups [25]. Also, the experiments carried out on 30 rodents indicated that brain injury results in a reduction of *IQ* values [49]. Furthermore, the hypothermic rats showed greater average *IQ* than normothermic rats for various injury levels, confirming that hypothermia accelerates brain's electrical recovery after CA. In another study of 28 rats, *IQ* values at 30-min post-CA also showed a strong correlation with 72-h NDS [19]. These results demonstrate the efficacy of the *IQ* at prognostication of CA outcome for hypothermia.

3.3.2 Subband information quantity

As discussed in Sect. 3.3.1., *IQ* measures information of the gross EEG signal in all frequency bands from delta to gamma. However, brain recovery from CA may be more related to the activities of individual EEG subbands. In fact, a more recent study on rats indicated that *IQ* prognostication sensitivity may degrade over time by overestimating the CA outcome at later period of recovery [50]. In contrast to *IQ*, subband information quantity (*SIQ*) calculates the information content within each k th subband of a r-level DWT separately:

$$SIQ^k(n) = -\sum_{m=1}^{M} p_m^k(n)\log_2(p_m^k(n)), \quad (13)$$

where $k = 1, 2, ..., r + 1$. Note that $p_m^k(n)$ is the probability that the sampled signal in k th subband belongs to the interval $\{I_m : m = 1, 2, ..., M\}$, and it is obtained as the ratio between the number of the samples found within interval I_m and the total number of samples in kth subband.

Then the overall *SIQ* is calculated by averaging the individual subband information quantities over all subbands of interests:

$$SIQ(n) = -\sum_{k=1}^{r+1} SIQ^k(n). \quad (14)$$

The examination of *IQ* and *SIQ* trends in a rodent hypothermia study indicated that *SIQ* values were more highly correlated (correlation of 0.74 vs. 0.65) with 72-h post-CA NDS than *IQ* values. It was also revealed that the most significant variations of *SIQ* were contributed by Theta, Beta, and Alpha bands.

Another study on 36 rats showed that the *SIQ* value was significantly higher when hypothermia was administered immediately post-resuscitation and maintained for 6-h relative to when hypothermia started 1 h post-resuscitation and maintained 12 h [51]. Also in a study of 14 rats, Deng. et al. showed that both *IQ* and *SIQ* at 1-h post-CA had high correlation (0.8) with 72-h NDS scores [52].

In another study of 27 rats by the same group, the Gamma-band *SIQ* values showed the highest correlation with 72-h NDS at every time point from 30-min to 72-h post-ROSC, while the Delta-band *SIQ* showed the lowest correlation to the CA outcome [53].

3.4 Combined measures

3.4.1 Cerebral recovery Index

Given the promising results of CA outcome predictions using single quantitative EEG measures (features), one could possibly enhance the accuracy in prognostication by using a combination of multiple features. Within this context, Tjepkema-Cloostermans et al. employed a set of EEG features to define a single number index, called cerebral recovery index (*CRI*), for the prognostication of outcome in CA patients treated with hypothermia [54]. Motivated by the criteria generally employed by the neurologists for visual inspection of EEG patterns, the authors chose the following five EEG features:

– *SD*: Standard deviation of the EEG signal over 5-min epochs were used as a measure of the signal power.
– H_{sh}: Shannon entropy of the signal was calculated where the values of p_i in Eq. (1) were determined using a histogram of the amplitude of the signal with 1 μV bin-width over the range of (− 200 to 200 μV).
– *ADR*: The EEG signal ratio between Alpha-band (8–13 Hz) and Delta-band (0.5–4Hz) was obtained from power spectrum analysis of the signal.
– *COH*: The mean coherence in the Delta-band between all possible combinations of EEG channels was used as a measure to quantify EEG patterns with abnormally high synchronization level.
– *REG*: Finally, to differentiate burst suppression from continuous EEG patterns, a new regularity measure (*REG*) was introduced. For this purpose, first a non-negative smoothed version of the EEG signal was obtained by applying a 0.5-s moving-average filtering to the square of the signal $\{s^2(i)|i = 1, ..., N\}$. Then the values of the smoothed signal were sorted in descending order (let us call this sorted smoothed signal as $\{q(i)|i = 1, ...N\}$) and the normalized standard deviation of the sorted values was calculated as

$$REG = \sqrt{\frac{\sum_{i=1}^{N} i^2 q(i)}{\frac{1}{3}N^2 \sum_{i=1}^{N} q(i)}} \tag{15}$$

REG range of values is between 0 and 1. An EEG signal with shorter bursts would result in smaller values of *REG*, while values closer to 1 indicate a signal with longer bursts.

Following the calculation of above features, they were normalized using a sigmoidal transform function whose coefficients were selected heuristically [10]. Given the significance of the role of the EEG signal power (*SD*) as an indicator of brain's recovery, the cerebral recovery index was defined as

$$CRI = \frac{SD(H_{sh} + ADR + COH + REG)}{4}. \tag{16}$$

The study of 109 hypothermic CA patients showed that the calculated *CRI* at 24-h post-CA can differentiate the dichotomized good outcome (CPC score of 1 or 2) versus poor outcome (CPC score of above 3) with the following accuracies: *CRI* < 0.29 predicted the poor outcome with sensitivity of 55% and specificity of 100%, while *CRI* > 0.69 predicted the good outcome with sensitivity of 25% and specificity of 100%.

3.4.2 Enhanced cerebral recovery index

In a recent study, Ghassemi et al. [10] introduced an enhanced version of cerebral recovery index (*ECRI*) by including the following additional features:

– Tsalis entropy area (*TsEnA*): Tsalis entropy is a nonextensive statistics to quantify the regularity of a signal [55], and is defined as

$$TsEn = \frac{1 - \sum_{i=1}^{N} (p_i)^q}{1 - q}, \tag{17}$$

where q is the nonextensivity degree. Comparing to conventional measures of entropy, *TsEn* can better describe the quasi-stationary properties of weakly ergodic systems in long-ranging interactions [55]. Since EEG signal is the result of long-ranging interactions across corticothalamic and thalamocortical networks [56], in general, *TsEn* may be able to provide more detailed information on EEG spikes and bursts, relative to other traditional entropy measures. To predict the CA arrest outcomes in a rodent model (with no hypothermia), Zhang et al. defined a new Tsalis entropy-based measure named Tsalis entropy area (*TsEnA*) to quantify the complex dynamics of burst suppression in EEG after CA [57]:

$$TsEnA = \sum_{t_1}^{t_2} \frac{N^{1-q} + \sum_{i=1}^{N} (p_i)^q}{1 - q} \text{ for } q \neq 1 \tag{18}$$

where t_1 and t_2 are the starting and ending times of burst suppression. Using a smooth histogram of the amplitude of the signal with $N = 50$, and $q = 3$, the authors achieved a high correlation of 0.86 between *TsEnA* values and 72-h post-ROSC NDS scores. Given the success of this study, Ghassemi et al. used *TsEnA* with $q = 2$ as one of the features to predict CA outcome in patients undergoing hypothermia.

– Cepstrum coefficients (*CP*) is the inverse of the Fourier transform of the log-magnitude of the spectrum of the signal [58]. *CP* provides information about rate of change in different spectrum bands and is widely used as a feature vector in signal processing.

– Maximum phase lag index (PLI_{Max}) across all EEG channels was used as a measure of connectivity/synchronization. It is known that the phase lag index characterizes the asymmetry of the distribution of phase differences $\Delta\phi$ between two signals [59] and can be calculated as

$$PLI = \left| < Sign[\Delta\phi(t_i)] > \right|, \tag{19}$$

where $\{t_i | i = 1, ..., N\}$ are the time indices. PLI is within the range of zero to one. A value of zero indicates either no coupling or coupling with $\Delta\phi$ centered around $0 \bmod \pi$, while a value of one means phase locking at a $\Delta\phi$ different than $0 \bmod \pi$. Ghassemi et al. used the maximum values of PLI over all EEG channels as one of the additional features for CA outcome prediction.

– A binary low voltage state measure to detect the EEG less than 1 µV.

A logistic regression model was applied to the aforementioned EEG features to obtain the enhanced cerebral recovery index (*ECRI*) and to estimate a dichotomized CPC score at discharge (CPC scores of 1–2 vs. CPC scores of 3–5). A one-leave-out cross-evaluation of the proposed method on EEG data of 167 CA patients spanning from three institutions revealed that (comparing to *CRI*) the *ECRI* increased the accuracy of prognostication in the first 24-h post-CA by an average of 27%.

These results confirm the efficacy of employing the combined features in prognostication of CA outcome for the patients undergoing the hypothermia.

3.4.3 Bispectral Index

Bispectral index (BIS) is a quantitative measure of EEG that is measured by a commercially available device from ASPECT Medical Systems Inc., MA, USA. The first version of the product entered the market in 1994, and since then BIS monitors have undergone various updates both in terms of software and hardware. Frontotemporal adhesive sensors are used to capture the surface EEG, then a weighted sum of several EEG features are obtained (including frequency below which 95% of the power spectrum resides, the relative beta ratio, BSR, and a measure of EEG phase coupling), and then a number in the range of 0–100 is reported to indicate the level of awareness [48]. BIS is simple to apply, however the exact algorithm to calculate the index is proprietary information. In fact, the use of BIS monitors to track the hypnotic component of anesthesia has been controversial at times [45].

Several recent studies have been able to use BIS for the prediction of CA outcome for the patients undergoing hypothermia. The majority of these studies have revealed that the mean BIS values are significantly lower in the patients with poor outcomes (CPC of 1 and 2) [48, 60–67]. A BIS

cutoff-point in a range of 35–45 has shown an accuracy above 0.85 in prediction of the poor outcome [60, 61, 63, 65, 67]. More details about the results of these studies can be found in Table 2.

4 Discussion and conclusion

Early and accurate assessment of brain recovery and neurological outcome after CA can substantially help with the optimal healthcare management of the CA patients, and minimizing related emotional and financial costs for their families. Over the last few decades, several prognostication markers of CA outcome have been developed using various modalities including clinical examination, biochemical markers, electrophysiological testing, and neuroimaging [9]. Clinical examination outcomes such as the absence of motor response to painful stimuli, presence of myoclonus status epilepticus, and lack of brainstem reflexes have been widely used for CA prognostication [17, 68]. Biochemical markers of cerebral injury such as increased levels of lactate and Neuron-Specific Enolase (NSE) have been employed to predict the CA outcome, as well [69, 70]. The loss of distinction between gray and white matter measured by computer tomography (CT) [71], or reduced glucose metabolism detected by position emission tomography (PET) are other potential prognostication markers of CA outcome [72].

Hypothermia is shown to be one of the most effective neuroprotective methods for improving the CA functional outcome in animal models of global ischemia [33, 73, 74] and human clinical trials [75, 76]. Moderate hypothermia is the process of reducing the body core temperature to a range of about 32–34 °C (90–93 °F), and maintaining it for 12–24 h, to ensure organ perfusion and oxygenation [77]. However, the use of sedative and paralytic agents affects sensitivity of the conventional CA prognostication markers and changes their optimal timing for the outcome prediction [7, 9, 11–15]. Hence, currently there is no universally accepted method for CA outcome prognostication of the patients treated with hypothermia [7].

EEG monitoring has been shown to be useful in early CA outcome prediction [78], but the subjective and time-consuming visual EEG interpretation limits its applicability as the preferred prognostic method. Automatic EEG pattern recognition using quantitative measures of EEG can overcome these barriers [54]. Thus, over the last few years there has been a growing interest in development and study of quantitative EEG prognostication markers [42]. Given the applicability of EEG monitoring and the significance of hypothermia in the prognostication of the CA outcome, in this work, we reviewed the existing literature on the employment of the quantitative measures of EEG to predict the outcome of CA in the patients treated with hypothermia.

An injury to the brain system can adversely affect its complexity. Thus, the use of entropy (a measure of system's complexity) may assist in tracking the recovery status of the brain after CA. Given this premise, a majority of the developed CA prognostication markers are entropy-based. Spectrum entropy, approximate entropy, multiple Scale entropy, and Wavelet subband entropy have all proved to be useful in CA outcome prediction for the subjects undergoing hypothermia [18, 21, 26, 28, 33]. In general, higher values of these entropy-based measures have been shown to be associated with better neurological outcomes. Among the features, multiple scale entropy and Wavelet subband entropy can provide a more comprehensive characterization of the signal's complexity, as they include more spatiotemporal information. However, they require higher computational complexity which may be an issue for automatic real-time EEG analysis.

A clinically accepted marker of brain injury is burst suppression activity in EEG [57]. Few burst suppression features have been successfully employed for CA outcome prediction during hypothermia [21, 28, 33]. Lower burst suppression ratio and higher burst suppression frequency have been generally associated with better outcomes.

Information quantity-based measures have demonstrated better tracking capability for both frequency changes and dynamic amplitude changes relative to conventional entropy-based measures [19, 49, 52, 53]. Brain injury results in a reduction of information quantity, and thus, higher values of information quantity are associated with better outcomes.

It is well-known that brain is a non-linear time-variant system, and EEG is a quasi-periodic and non-stationary signal. Thus, a single EEG feature may only provide limited information about the status of such a complicated system. On the other hand, combining EEG features may improve the accuracy of CA prognostication. The original cerebral recovery index and its enhanced version were developed based on this premise [10, 54]. Although these two indices have demonstrated some promising results in CA outcome prediction, their further enhancement in terms of prediction sensitivity is needed to be clinically acceptable.

Currently, there are few commercially available products to extract the EEG features. For example, the entropy module of Datex-Ohmeda (GE Healthcare, Helsinki, Finland) can be used to extract state entropy, relative entropy, and BSR. BIS monitors by ASPECT medical systems, MA, USA can also extract BSR and BIS values. These commercially available monitors are simple to use by clinicians. However, some degree of variability among different monitors/models and consequently the extracted feature values should be expected, especially because some of these products (e.g., BIS monitors) have undergone various software/hardware updates throughout the years. In general, significantly lower BIS values have been associated with poor outcome (CPC of 1 and 2) in CA patients [48, 60–67], and a BIS cutoff-point in the range of 35–45 has shown an accuracy of above 0.85 in prediction of the poor outcome in patients treated with hypothermia [60, 61, 63, 65, 67].

One potential approach to design a highly accurate CA outcome classification system is to apply advanced machine learning algorithms (e.g., support vector machines, decision trees) to a large vector of various EEG features (including those measured by commercially available products). Recent advancements in data mining techniques have enabled the efficient handling of the inherent variability in the extracted features (such as those due to employment of different BIS monitors). Inclusion of quantitative features from other modalities (e.g., biochemical markers or neuroimaging) could further enhance the classification accuracy [9, 21, 64]. For example, in [21], Wennervirta et al. showed that the accuracy of CA outcome prediction can be considerably improved by combining a biochemical marker (protein 100B) and an EEG feature (wavelet subband entropy). However, their small cohort study prevented them from performing statistically reliable techniques such as cross-validation to validate their prediction accuracy on an independent dataset. In a larger study cohort (75 patients), Stammet et al. were able to enhance the accuracy of CA outcome prediction by more than 5% (statistically significant) with combining the S100B and BIS information [64] .

In general, the reliable implementation of machine learning approaches requires a large dataset of CA subjects with clear documentation of physiological and clinical data following CA. A potential solution to overcome this challenge is the conduct of multi-institution research collaborations where the multimodality data is consistently and uniformly collected and shared among researchers to facilitate the development of reliable methods to predict the CA outcome.

Compliance with ethical standards

References

1. Nichol G, Thomas E, Callaway CW, Hedges J, Powell JL, Aufderheide TP, et al. Regional variation in out-of-hospital cardiac arrest incidence and outcome. JAMA. 2008;300:1423–31.
2. Stecker EC, Reinier K, Marijon E, Narayanan K, Teodorescu C, Uy-Evanado A, et al. Public health burden of sudden cardiac death in the United States. Circulation. 2014. https://doi.org/10.1161/CIRCEP.113.001034
3. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Executive summary: heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation. 2010;121:948–54.
4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary. Circulation. 2015;131:434–41.
5. Geocadin RG, Buitrago MM, Torbey MT, Chandra-Strobos N, Williams MA, Kaplan PW. Neurologic prognosis and withdrawal of life support after resuscitation from cardiac arrest. Neurology. 2006;67:105–8.
6. Lim C, Alexander MP, LaFleche G, Schnyer DM, Verfaellie M. The neurological and cognitive sequelae of cardiac arrest. Neurology. 2004;63:1774–8.
7. Samaniego EA, Persoon S, Wijman CA. Prognosis after cardiac arrest and hypothermia: a new paradigm. Curr Neurol Neurosci Rep. 2011;11:111–9.
8. Storm C, Steffen I, Schefold JC, Krueger A, Oppert M, Jörres A, et al. Mild therapeutic hypothermia shortens intensive care unit stay of survivors after out-of-hospital cardiac arrest compared to historical controls. Crit Care. 2008;12:R78.
9. Karapetkova M, Koenig MA, Jia X. Early prognostication markers in cardiac arrest patients treated with hypothermia. Euro J Neurol. 2015;23:476–88
10. Ghassemi MM, Amorim E, Pati SB, Mark RG, Brown EN, Purdon PL, et al. An enhanced cerebral recovery index for coma prognostication following cardiac arrest. In 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2015, pp. 534–537.
11. Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol. 2010;67:301–7.
12. Al Thenayan E, Savard M, Sharpe M, Norton L, Young B. Predictors of poor neurologic outcome after induced mild hypothermia following cardiac arrest. Neurology. 2008;71:1535–7.
13. Rundgren M, Westhall E, Cronberg T, Rosen I, Friberg H. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med. 2010;38:1838–44.
14. Rittenberger JC, Popescu A, Brenner RP, Guyette FX, Callaway CW. Frequency and timing of nonconvulsive status epilepticus in comatose post-cardiac arrest subjects treated with hypothermia. Neurocrit Care. 2012;16:114–22.
15. Crepeau AZ, Rabinstein AA, Fugate JE, Mandrekar J, Wijdicks EF, White RD, et al. Continuous EEG in therapeutic hypothermia after cardiac arrest Prognostic and clinical value. Neurology.2013;80:339–44.
16. Snyder BD, Hauser WA, Loewenson RB, Leppik IE, Ramirez-Lassepas M, Gumnit RJ. Neurologic prognosis after cardiopulmonary arrest: III. Seizure activity. Neurology. 1980;30:1292–7.
17. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;67:203–10.
18. Moshirvaziri H, Ramezan-Arab N, Asgari S Prediction of the outcome in cardiac arrest patients undergoing hypothermia using EEG wavelet entropy. In 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), 2016, pp. 3777–80.
19. Jia X, Koenig MA, Nickl R, Zhen G, Thakor NV, Geocadin RG. Early electrophysiologic markers predict functional outcome associated with temperature manipulation after cardiac arrest in rats. Crit Care Med. 2008;36:1909–16.
20. Koenig MA, Kaplan PW, Thakor NV. Clinical neurophysiologic monitoring and brain injury from cardiac arrest. Neurol Clin. 2006;24:89–106.
21. Wennervirta JE, Ermes MJ, Tiainen SM, Salmi TK, Hynninen MS, Sarkela MO, et al. Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity". Crit Care Med. 2009;37:2427–35.
22. Viertio-Oja H, Maja V, Sarkela M, Talja P, Tenkanen N, Tolvanen-Laakso H, et al., Description of the entropy algorithm as applied in the Datex-Ohmeda S/5 entropy module. Acta Anaesthesiol Scand. 2004;48:154–61.
23. Yang Q, Su Y, Hussain M, Chen W, Ye H, Gao D, et al. Poor outcome prediction by burst suppression ratio in adults with postanoxic coma without hypothermia. Neurol Res. 2014. https://doi.org/10.1179/1743132814Y.0000000346.
24. Levy WJ, Pantin E, Mehta S, McGarvey M. Hypothermia the approximate entropy of the electroencephalogram. Anesthesiology. 2003;98:53–7.
25. Jia X, Koenig MA, Shin HC, Zhen G, Yamashita S, Thakor NV, et al., Quantitative EEG and neurological recovery with therapeutic hypothermia after asphyxial cardiac arrest in rats. Brain Res. 2006;1111:166–75.
26. Kang X, Jia X, Geocadin RG, Thakor NV, Maybhate A. Multiscale entropy analysis of EEG for assessment of post-cardiac arrest neurological recovery under hypothermia in rats. IEEE Trans Biomed Eng. 2009;56:1023–31.
27. Dandan Z, Jia X, Ding H, Ye D, Thakor NV. Application of Tsallis entropy to EEG: quantifying the presence of burst suppression after asphyxial cardiac arrest in rats. IEEE Trans Biomed Eng. 2010;57:867–74.
28. Noirhomme Q, Lehembre R, Lugo Zdel R, Lesenfants D, Luxen A, Laureys S, et al. Automated analysis of background EEG and reactivity during therapeutic hypothermia in comatose patients after cardiac arrest. Clin EEG Neurosci. 2014;45:6–13.
29. Deboer T. Brain temperature dependent changes in the electroencephalogram power spectrum of humans and animals. J Sleep Res. 1998;7:254–62.
30. Borda M. Fundamentals in information theory and coding. Berlin: Springer; 2011.
31. Seely AJ, Macklem PT. Complex systems and the technology of variability analysis. Crit Care. 2004;8:R367.
32. Tong S, Bezerianos A, Paul J, Zhu Y, Thakor N. Nonextensive entropy measure of EEG following brain injury from cardiac arrest". Phys A. 2002;305:619–28.
33. Chen B, Song FQ, Sun LL, Lei LY, Gan WN, Chen MH, et al., Improved early postresuscitation EEG activity for animals treated with hypothermia predicted 96 hr neurological outcome and survival in a rat model of cardiac arrest. Biomed Res Int. 2013. https://doi.org/10.1155/2013/312137
34. Ajam K, Gold LS, Beck SS, Damon S, Phelps R, Rea TD. Reliability of the Cerebral Performance Category to classify neurological status among survivors of ventricular fibrillation arrest: a cohort study. Scand J Trauma Resusc Emerg Med. 2011;19:38.
35. Ho KK, Moody GB, Peng CK, Mietus JE, Larson MG, Levy D, et al. Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics. Circulation. 1997;96:842–8.

36. Pincus SM Approximate entropy as a measure of system complexity. Proc Natl Acad Sci. 1991;88:2297–2301.
37. Grassberger P. Information and complexity measures in dynamical systems in Information dynamics. New York: Springer; 1991, pp. 15–33.
38. Costa M, Goldberger AL, Peng C-K. Multiscale entropy analysis of complex physiologic time series. Phys Rev Lett. 2002;89:068102.
39. Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol. 2000;278:H2039–49.
40. Steriade M, Llinás RR. The functional states of the thalamus and the associated neuronal interplay. Physiol Rev. 1988;68:649–742.
41. Katz L, Ebmeyer U, Safar P, Radovsky A, Neumar R. Outcome model of asphyxial cardiac arrest in rats. J Cereb Blood Flow Metab. 1995;15:1032–9.
42. Geocadin R, Ghodadra R, Kimura T, Lei H, Sherman D, Hanley D, et al. A novel quantitative EEG injury measure of global cerebral ischemia. Clin Neurophysiol. 2000;111:1779–87.
43. Shen EH, Cai ZJ, Gu FJ. Mathematical foundation of a new complexity measure. Appl Math Mech. 2005;26:1188–96.
44. Lu Y, Jiang D, Jia X, Qiu Y, Zhu Y, Thakor N, et al. Predict the neurological recovery under hypothermia after cardiac arrest using C0 complexity measure of EEG signals. In Engineering in Medicine and Biology Society, 2008. EMBS 2008. 30th Annual International Conference of the IEEE, 2008, pp. 2133–6.
45. Sarkela MO, Ermes MJ, van Gils MJ, Yli-Hankala AM, Jantti VH, Vakkuri AP. Quantification of epileptiform electroencephalographic activity during sevoflurane mask induction. Anesthesiology. 2007;107:928–38.
46. Bhattacharyya S, Biswas A, Mukherjee J, Majumdar AK, Majumdar B, Mukherjee S, et al. Detection of artifacts from high energy bursts in neonatal EEG. Comput Biol Med. 2013;43:1804–14.
47. Sarkela M, Mustola S, Seppanen T, Koskinen M, Lepola P, Suominen K, et al. Automatic analysis and monitoring of burst suppression in anesthesia. J Clin Monit Comput. 2002;17:125–34.
48. Seder DB, Dziodzio J, Smith KA, Hickey P, Bolduc B, Stone P, et al. Feasibility of bispectral index monitoring to guide early post-resuscitation cardiac arrest triage. Resuscitation. 2014;85:1030–6.
49. Shin H-C, Tong S, Yamashita S, Jia X, Geocadin G, Thakor V. Quantitative EEG and effect of hypothermia on brain recovery after cardiac arrest. IEEE Trans Biomed Eng. 2006;53:1016–23.
50. Shin H-C, Jia X, Nickl R, Geocadin RG, Thakor NV. A sub-band-based information measure of EEG during brain injury and recovery after cardiac arrest. IEEE Trans Biomed Eng. 2008;55:1985–90.
51. Jia X, Koenig MA, Shin H-C, Zhen G, Pardo CA, Hanley DF, et al. Improving neurological outcomes post-cardiac arrest in a rat model: immediate hypothermia and quantitative EEG monitoring. Resuscitation. 2008;76:431–42.
52. Deng R, Young LM, Jia X. Quantitative EEG markers in severe post-resuscitation brain injury with therapeutic hypothermia. In Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE, 2015, pp. 6598–601.
53. Deng R, Koenig MA, Young LM, Jia X. Early quantitative gamma-band EEG marker is associated with outcomes after cardiac arrest and targeted temperature management. Neurocrit. Care. 2015;23:262–73.
54. Tjepkema-Cloostermans MC, van Meulen FB, Meinsma G, van Putten MJ. A Cerebral Recovery Index (CRI) for early prognosis in patients after cardiac arrest. Crit Care. 2013;17:1.
55. Tsallis C. Possible generalization of Boltzmann-Gibbs statistics. J Stat Phys. 1988;52:479–87.
56. Contreras D, Destexhe A, Sejnowski TJ, Steriade M. Spatiotemporal patterns of spindle oscillations in cortex and thalamus. J Neurosci. 1997;17:1179–96.
57. Zhang D, Jia X, Ding H, Ye D, Thakor NV. Application of Tsallis entropy to EEG: quantifying the presence of burst suppression after asphyxial cardiac arrest in rats. IEEE Trans Biomed Eng. 2010;57:867–74.
58. Proakis JG, Manolakis DG. Digital signal processing (4th ed.). Upper Saddle River, N.J.: Pearson Prentice Hall; 2007.
59. Stam CJ, Nolte G, Daffertshofer A. Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Human Brain Mapp. 2007;28:1178–93.
60. Seder DB, Fraser GL, Robbins T, Libby L, Riker RR. The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Intensive Care Med. 2010;36:281–8.
61. Leary M, Fried DA, Gaieski DF, Merchant RM, Fuchs BD, Kolansky DM, et al. Neurologic prognostication and bispectral index monitoring after resuscitation from cardiac arrest. Resuscitation. 2010;81:1133–7, .
62. Riker RR, Stone PC Jr, May T, McCrum B, Fraser GL, Seder D. Initial bispectral index may identify patients who will awaken during therapeutic hypothermia after cardiac arrest: a retrospective pilot study. Resuscitation. 2013;84:794–7.
63. Selig C, Riegger C, Dirks B, Pawlik M, Seyfried T, Klingler W. Bispectral index (BIS) and suppression ratio (SR) as an early predictor of unfavourable neurological outcome after cardiac arrest. Resuscitation. 2014;85:221–6.
64. Stammet P, Wagner DR, Gilson G, Devaux Y. Modeling serum level of s100beta and bispectral index to predict outcome after cardiac arrest. J Am Coll Cardiol. 2013;62:851–8.
65. Stammet P, Collignon O, Werer C, Sertznig C, Devaux Y. Bispectral index to predict neurological outcome early after cardiac arrest. Resuscitation. 2014;85:1674–80.
66. Jouffroy R, Lamhaut L, Guyard A, Philippe P, An K, Spaulding C, et al. Early detection of brain death using the Bispectral Index (BIS) in patients treated by extracorporeal cardiopulmonary resuscitation (E-CPR) for refractory cardiac arrest. Resuscitation. 2017;120:8–13.
67. Ochiai K, Shiraishi A, Otomo Y, Koido Y, Kanemura T, Honma M. Increasing or fluctuating bispectral index values during post-resuscitation targeted temperature management can predict clinical seizures after rewarming. Resuscitation. 2017;114:106–12.
68. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-lschemic coma. JAMA. 1985;253:1420–6.
69. Zandbergen E, Hijdra A, Koelman J, Hart A, Vos P, Verbeek M, et al. Prediction of poor outcome within the first 3 days of postanoxic coma. Neurology. 2006;66:62–8.
70. Anand N, Stead LG. Neuron-specific enolase as a marker for acute ischemic stroke: a systematic review. Cerebrovasc Dis. 2005;20:213–9.
71. Scheel M, Storm C, Gentsch A, Nee J, Luckenbach F, Ploner CJ, et al. The prognostic value of gray-white-matter ratio in cardiac arrest patients treated with hypothermia. Scand J Trauma, Resusc Emerg Med. 2013;21:23.
72. Rudolf J, Ghaemi M, Ghaemi M, Haupt WF, Szelies B, Heiss W-D. Cerebral glucose metabolism in acute and persistent vegetative state. J Neurosurg Anesthesiol. 1999;11:17–24.
73. Welsh FA, Sims RE, Harris VA. Mild hypothermia prevents ischemic injury in gerbil hippocampus. J Cereb Blood Flow Metab. 1990;10:557–63.
74. Minamisawa H, Smith ML, Siesjo BK. The effect of mild hyperthermia and hypothermia on brain damage following 5, 10, and 15 minutes of forebrain ischemia. Ann Neurol. 1990;28:26–33.

75. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med. 2002;346:557–63.

76. Fugate JE, Wijdicks EF, Mandrekar J, Claassen DO, Manno EM, White RD, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. Ann Neurol. 2010;68:907–14.

77. Deakin CD, Nolan JP, Soar J, Sunde K, Koster RW, Smith GB, et al. European resuscitation council guidelines for resuscitation 2010 Sect. 4. Adult advanced life support. Resuscitation. 2010;81:1305–52.

78. Cloostermans MC, van Meulen FB, Eertman CJ, Hom HW, van Putten MJ. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. Crit Care Med. 2012;40:2867–75.