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Early Quantitative Gamma-Band EEG Marker is Associated with Outcomes after Cardiac Arrest and Targeted Temperature Management

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Abstract

Background—Brain recovery after cardiac arrest (CA) is sensitive to temperature. Yet the effect of temperature management on different EEG frequency bands has not been elucidated. A novel quantitative EEG algorithm, sub-band information quantity (SIQ), was applied to evaluate EEG recovery and outcomes after CA.

Methods—24 Wistar rats undergoing 7-min CA were randomly assigned to immediate hypothermia (32–34°C), normothermia (36.5–37.5°C), or hyperthermia (38.5–39.5°C) (N=8). EEG was recorded continuously for the first 8 hrs and then for serial 30-min epochs daily. The Neurologic Deficit score (NDS) at 72-hr was the primary functional outcome. Another 4 rats without brain injury were added as a control.

Results—Better recovery of gamma-band SIQ was found in the hypothermia group (0.60±0.03) compared with the normothermia group (0.40±0.03) ($p<0.01$) and in the normothermia group compared with the hyperthermia group (0.34±0.03) ($p<0.05$). The NDS was also improved in the lower temperature groups: hypothermia [median (25th, 75th), 74 (61, 74)] versus normothermia [49 (47, 61)] versus hyperthermia [43 (0, 50)] ($p<0.01$). Throughout the 72-hr experiment, the gamma-band SIQ showed the strongest correlation at every time point (ranging 0.520–0.788 from 30-min to 72-hr post-resuscitation, all $p<0.05$) whereas the delta-band SIQ had poor correlation with the

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72-hr NDS. No significant difference of subband EEG was found with temperature manipulation alone.

Conclusions—Recovery of gamma-band SIQ-qEEG was strongly associated with functional outcomes after CA. Induced hypothermia was associated with faster recovery of gamma-band SIQ and improved functional outcomes. Targeted temperature management primarily affected gamma frequency oscillations but not delta rhythm.

Keywords

Cardiac arrest; Targeted temperature management; Hypothermia; EEG; Gamma-band EEG; Functional outcome

Introduction

Cardiac arrest (CA) has a prevalence of approximately 424,000 cases annually in the United States [1]. However, only 10.4% of out-of-hospital and 22.7% of in-hospital CA resulted in survival in 2014 [1] and surviving patients are susceptible to secondary neurological injuries. Minor fluctuations in temperature can severely affect ischemic cerebral pathological injury after CA [2]. Therapeutic hypothermia and avoidance of fever have been demonstrated to improve neurological outcome and survival [3–6].

Due to the limitations in detecting brain injury with standard clinical examination and structural imaging in comatose CA survivors, electroencephalography (EEG) has emerged as a widely used electrophysiological tool for prognostication [7, 8]. EEG measures the sum of synchronous activity of neuronal ensembles with similar spatial orientation. Berger [9] first described alpha waves and demonstrated that EEG is characterized by different rhythms. Subsequently, a number of studies were performed to investigate the frequency content of EEG for clinical diagnostic applications. In clinical practice, the EEG frequency bands of interests are defined as gamma (> 30 Hz), beta (16–30 Hz), alpha (8–15 Hz), theta (4–8 Hz), and delta (below 4 Hz) [10]. The neuronal oscillatory activities in each band represent coordinated activity [10] related to brain behavioral responses. The gamma-band, in particular, is associated with higher cortical functions such as learning, memory, perception, and consciousness [11, 12]. Therefore, recovery of gamma-band activity is a pivotal target for post-CA research related to neurological recovery.

Analysis of EEG is laborious and confounded by subjective interpretation and manual pattern recognition. Quantitative EEG (qEEG) has shown promising results in studying brain injury and recovery after CA [13, 14]. Based on information theory, the qEEG algorithm Information Quantity (IQ) was established in our previous studies [14] to provide an objective measure of the impact of temperature on neurological recovery after CA [13]. However, IQ was only used to quantify changes in the gross EEG signal. Because changes in each EEG frequency band may relate to recovery of different brain functions, we developed the sub-band IQ (SIQ) algorithm by averaging the SIQ in 5 frequency sub-bands (referred to below as conventional SIQ) [15]. We previously found that a lower conventional SIQ is associated with greater injury and poor neurological outcome after CA [15].

The recovery of SIQ in different EEG sub-bands after CA and the impact of temperature have not been elucidated. Because gamma-band activity is increased with higher cortical processes, we hypothesized that gamma-band SIQ would be strongly associated with functional outcome after CA. Second, we hypothesized that hypothermia would be associated with better recovery of gamma-band SIQ compared to normothermia and hyperthermia.

Materials and Methods

Animals

We evaluated the effect of hypothermia ($33\pm1^{\circ}\text{C}$), normothermia ($37\pm0.5^{\circ}\text{C}$), and hyperthermia ($39\pm0.5^{\circ}\text{C}$) in a rodent CA model. Twenty-four adult male Wistar rats (300–350 g, Charles River, Wilmington, MA) were randomly assigned to one of three groups: hypothermia, normothermia, or hyperthermia ($n=8$ per group). All 24 animals underwent 7-min asphyxial CA and resuscitation followed by immediate temperature management during recovery in accordance with their assigned group. Another 4 rats were assigned to an uninjured control group to explore whether temperature alone would alter the distribution of EEG subbands. All procedures were approved by The Johns Hopkins University Animal Care and Use Committee.

Cardiac Arrest and Temperature Management

The CA and resuscitation procedures were performed as previously described [13, 14, 16, 17]. Briefly, rats were intubated and ventilated with a pressure controlled ventilator. The animals were anesthetized with 1.0% halothane in 50%N₂/50%O₂ via the ventilator. The femoral artery and vein were cannulated to obtain sample arterial blood gases (ABG), continuously monitor blood pressure, and to deliver drugs. A 5-min EEG baseline measurement with halothane was recorded, followed by a 5-min washout period without halothane to eliminate the effect of the anesthetic on the EEG recording [14]. To induce paralysis, vecuronium (2mg/kg) was administered during the final 2 minutes of the washout period. Asphyxia was then induced by clamping the breathing circuit and stopping mechanical ventilation for 7 mins, thereby causing CA (pulse pressure $<10\text{mmHg}$). Cardiopulmonary resuscitation was performed with effective ventilation, external chest compression, epinephrine, and NaHCO₃, until return of spontaneous circulation (ROSC, pulse pressure $>60\text{mmHg}$). In order to avoid the anesthesia effect on EEG, no anesthetic was provided after ROSC. The blood pressure was monitored until 2 hours after ROSC before decannulation.

Approximately 1 week before experiments, a telemetry temperature sensor (G2 Emitter 870–0010-01, Mini Mitter, Sun River, OR) was implanted into the peritoneal cavity to monitor the rat's core temperature. Temperature management (hypothermia or hyperthermia) was initiated immediately after ROSC and the target temperature was maintained for 6 hrs.

The hypothermia group was cooled to reach a target temperature of 33°C in 15 mins. Hypothermia was induced by a manual external cooling method using cold water and

alcohol mist. The core temperature was maintained between 32–34°C for 6 hrs, after which the rewarming process began. The core temperature of the rat was gradually increased from 33°C to 37°C over 2 hours by a heating lamp and a heating pad [13, 14].

The core temperature of the normothermia group was maintained at 36.5–37.5°C for 8 hrs after ROSC. All animals were kept inside a neonatal incubator (Isolette infant incubator model C-86, Air-Shields, Hatboro, PA) for the first 24 hrs after ROSC to maintain a constant temperature after resuscitation [13].

The hyperthermia group was warmed to reach a target temperature of 39°C in 15 mins. Hyperthermia was induced by a heating pad and automatic heating lamp (Thermalet TH-5, model 6333, Physitemp Instruments, Clifton, NJ). The core temperature was maintained between 38.5–39.5°C for 6 hrs, after which the animal underwent passive cooling from 39°C to normothermia over the course of 2 hrs [13].

Sampling Method and SIQ qEEG Analysis

Two-channel EEG signals were recorded for the first 8 hrs after ROSC for all temperature groups via epidural electrodes, which were placed over the frontal area (± 2 mm lateral and 2 mm anterior to bregma) and the occipital area (± 2 mm lateral and 2 mm posterior to bregma), with the ground electrode 2 mm posterior to lambda at the midline, one week before the experiment. The sampling rate was 250 Hz [13, 14]. At 24-, 48-, and 72-hrs after ROSC, serial 30-min EEG recordings were carried out in all animals. The noise in the signal was detected from WinDaq software (Dataq Instruments, Akron, OH) and MATLAB (MathWorks, Natick, MA) [13]. Signals containing artifact were eliminated manually in the final analysis.

We computed the information content in each individual EEG frequency band using our previously established SIQ algorithm [15]. Briefly, a sliding window technique was applied to the non-stationary EEG waveforms so that the waveform was divided into temporal windows. Then, a discrete wavelet transform was used to separate the signal into sub-bands and compute the wavelet coefficients in each sub-band window. The probability functions of the wavelet coefficients were then separately estimated for each sub-band. The SIQ for each sub-band was then calculated using the probability functions and the entropy formula. Lastly, the SIQ values of each sub-band were averaged over all sub-bands, which was defined as “conventional SIQ”. To compare SIQ among different groups, the SIQ values were normalized to their corresponding baseline values from the signal recorded before the initiation of CA. We calculated SIQ values at baseline (0-5 mins), CA period, every 30 mins until 4 h, 24 h, 48 h and 72 h after ROSC.

EEG Recording and Temperature Management in Uninjured Rats

In order to study whether temperature alone would affect the activities of EEG sub-bands, 4 male adult Wistar rats were included in a sham/control group. All experimental preparations were equivalent to CA-rats. All rats were anesthetized with 1.0% halothane in 1:1/N₂:O₂ during the continuous EEG recording. The rats were maintained at normothermia for 30 mins followed by a 15-min hypothermic transition period. The hypothermic core temperature was maintained for 1 hr, and the animals were then gradually warmed to

hyperthermia at the rate of 2°C/hr. The hyperthermic temperature was sustained for 1 hr. The EEG was continuously recorded during the experiment. The conventional SIQ as well as SIQs of all sub-bands were computed and compared among different temperature manipulations.

Neurologic Evaluation

The neurological condition of each rat was evaluated by a Neurological Deficit Scale (NDS) score with a range of 0-80 and higher numbers representing better function. The score is based on a series of behavioral tests [13, 14]. The NDS score of each animal was calculated after the recovery period on the day of CA and repeated at 24 hrs, 48 hrs and 72 hrs after ROSC. The trained examiner, blinded to temperature groups, determined the NDS score at all time points except on the day of CA. The 72-hr NDS was the primary indicator of functional outcome. We defined good functional outcome as rats with 72-hr NDS ≥ 60 and bad functional outcome as rats with 72-hr NDS < 60 after regrouping all rats irrespective of temperature group [13].

Statistical Analysis

Statistical analyses were performed using a commercial statistical computer program (IBM SPSS Statistics, version 22, Armonk, NY). The parametric test results of experimental groups were reported as mean $\pm$ S.E.M. whereas nonparametric test results were reported as median (interquartile range). "Aggregate SIQ" was defined as the SIQ signal analyzed over the 72-hr study period. Univariate analyses were performed to test for differences in SIQ values and 72-hr NDS outcomes between temperature groups. Nonparametric analysis of variance was conducted to determine the differences in NDS. The good electrophysiological outcome in each sub-band was predefined as a SIQ value greater than the mean SIQ in each temperature group at different time intervals. Bivariate analyses using the Pearson correlation were used to test for a correlation between 72-hr NDS and SIQ and the correlation between good or bad outcome using the recovery of 72-hr NDS and SIQ as defined above. A receiver operating characteristic (ROC) curve was used to identify the SIQ cutoff point with ideal sensitivity and specificity for good functional outcome (72-hr NDS ≥ 60). A value of $p < 0.05$ was considered to be significant.

Results

Temperature Management, Mortality and ABG Data

The core temperature was well controlled for all 24 rats. The three target temperatures - hypothermia ($33 \pm 1^\circ\text{C}$), normothermia ($37 \pm 0.5^\circ\text{C}$), and hyperthermia ($39 \pm 0.5^\circ\text{C}$) - were readily achieved and maintained as shown in Fig.1. The mortalities of hypothermia, normothermia and hyperthermia groups were 0%, 12.5% and 50%, respectively. There were no significant differences between the three groups in ABG data, including pH, PO₂, PCO₂ bicarbonate, and O₂ saturation (data not shown).

Aggregate SIQ was Associated with Post-CA Functional Outcomes

In the control group without CA, the SIQs of each sub-band and conventional SIQ were similar among the three temperature groups ($p > 0.05$) (Table.1), suggesting no alterations of

SIQs, especially conventional, gamma- and delta-band SIQ, were induced by temperature alone.

In the CA-rats, we converted the raw EEG signal to SIQ values (Fig.2). There were significant differences in aggregate SIQ values between the three temperature groups ($p<0.05$) (Table.1). Better recovery of aggregate conventional SIQ was found in the hypothermia group (0.80 ± 0.02) compared with the normothermia group (0.69 ± 0.02) ($p<0.01$) and in the normothermia group compared with the hyperthermia group (0.66 ± 0.02) ($p<0.05$). In the analysis of SIQ in each sub-band, the aggregate SIQ in the gamma-band showed the same tendency as conventional SIQ. Higher aggregate SIQ values in the gamma-band were found in the hypothermia group (0.60 ± 0.03) compared with the normothermia group (0.40 ± 0.03) ($p<0.01$) and in the normothermia group compared with the hyperthermia group (0.34 ± 0.03) ($p<0.05$). The recovery of conventional SIQ and gamma-band SIQ were consistent with the NDS (median (25th, 75th)) such that the hypothermia group had a higher NDS (74 (61, 74)) than the normothermia group (49 (47, 61)) ($p<0.01$) and the normothermia group had a higher NDS compared to the hyperthermia group (43 (0, 50)) ($p<0.01$). No seizures were recorded during NDS assessments.

Temporal Evolution of SIQ was Associated with Functional Outcomes in the Three Temperature Groups

There were significant differences in conventional SIQ (Fig. 3A) and sub-band SIQ values except delta SIQ (Fig.3C) among the three temperature groups as early as 30 mins after ROSC (Table. S1, $p<0.05$), with the most significant differences in gamma SIQ (Fig. 3B). Bivariate analyses showed no significant correlation between 72-hr NDS and SIQ value in the delta-band. However, significant correlations were found between the 72-hr NDS and conventional SIQ values, and SIQ values in all other sub-bands (Table.2) at 30 mins, 1 hr, 1.5 hrs, 2 hrs, and 2.5 hrs after ROSC. It should be noted that a significant correlation was found between 72-hr NDS and SIQ values at every time point between 30 mins and 72 hrs using the conventional SIQ, except at 4 hrs. The gamma-band SIQ showed a more robust significant correlation with 72-hr NDS at every time point after ROSC (30 mins, 0.555, $p<0.05$; 1 hr, 0.599, $p<0.01$; 1.5 hrs, 0.520, $p<0.05$; then ranging 0.649-0.788 for the remaining time points, all $p<0.01$) (Fig.4).

Good Functional Outcomes were Associated with Higher SIQ Values

All rats were categorized into good or bad functional outcome groups. There were 8 rats from the hypothermia group and 3 rats from the normothermia group in the good outcome group, whereas the bad outcome group consisted of 8 hyperthermic rats and 5 normothermic rats. By comparing the aggregate SIQ value (Fig.5A), animals with good functional outcomes at 72 hrs had higher conventional SIQ values (0.80 ± 0.02) compared to animals with bad functional outcomes (0.65 ± 0.02) ($p<0.01$). Among the sub-bands, rats with good functional outcomes had significantly higher SIQ values compared to those with bad functional outcomes in the theta-band (0.86 ± 0.02 versus 0.75 ± 0.02 , $p<0.01$), alpha-band (0.78 ± 0.02 versus 0.64 ± 0.02 , $p<0.01$), beta-band (0.69 ± 0.02 versus 0.51 ± 0.02 , $p<0.01$), and gamma-band (0.59 ± 0.03 versus 0.32 ± 0.02 , $p<0.01$). However, there was no significant difference in the SIQ values of the delta-band.

By comparing the temporal evolution of SIQ values (Table. S2), significant differences between animals with good and bad outcomes were seen in the high frequency bands (beta and gamma) from 30 mins to 72 hrs after ROSC except in the beta-band at 4 hrs, and in the intermediate frequency bands (theta and alpha) from 30 mins to 2.5 hrs after ROSC, with the alpha rhythm also showing significant differences at 3 hrs, 48 hrs and 72 hrs. Gamma-band SIQ (Fig.5C) and conventional SIQ (Fig.5B) most consistently discriminated between animals with good and bad functional outcomes at all time points from 30 mins to 72 hrs after ROSC. Conversely, the delta-band poorly discriminated between animals with good and bad outcomes at most time points after ROSC (except at 1.5 hrs) (Fig. 5D).

To study the relation between good electrophysiological recovery (defined as SIQ - mean SIQ) and good functional outcome (72-hr NDS ≥ 60), electrophysiological recovery was strongly correlated with good functional outcome starting from 30 mins after ROSC (Table. 2). The conventional SIQ recovery showed significant correlation with functional outcome at 1 hr, and 2 hrs to 72 hrs, with no significant correlation at 0.5 and 1.5 hrs. The gamma-band had the strongest correlation with functional outcome as significant correlation coefficients were identified from 30 mins to 72 hrs, while the delta-band had no correlation with functional outcome.

Predictive Value of SIQ-qEEG Values

Receiver operation characteristic (ROC) curves were used to identify the SIQ cut-off points at different intervals with optimal sensitivity and specificity for predicting good functional outcome at 72 hrs. The optimal SIQ cut-off points were defined by an area under the ROC curve > 0.8 and the highest specificity (100%) among all EEG sub-bands except delta. As shown in Table 2, the cut-off points with highest sensitivity of 0.909 appeared in conventional SIQ at 1-hr and in the alpha-band at 1.5-hr post-ROSC. However, among conventional SIQ and all sub-bands, the most consistently predictive cut-off points (from 30 min through 4 hrs and then daily until 72-hr) occurred in the gamma-band (from sensitivity of 0.273 at 30-min to 0.600 at 72-hr after ROSC). The most accurate gamma-band cut-off point was at 2 hrs after ROSC, where the SIQ > 0.39 had sensitivity of 0.727 and specificity of 100% for prediction of good functional outcome (Fig. 6).

Discussion

In this study, recovery of SIQ-qEEG signal was associated with better functional outcomes after resuscitation from CA and targeted temperature management led to sustained improvement of SIQ values soon after ROSC. The gamma-band had the strongest and most consistent association with outcome and temperature management compared to the other EEG sub-bands. Conversely, the delta-band represented a more constant component of EEG signal and showed no consistent association with outcome or temperature management. Temperature manipulation alone, without brain injury, was not found to be a confounder in this study. The alterations of EEG reported in this study were due to the effect of temperature management on the ischemic brain.

IQ was introduced in our prior studies to quantify EEG signal as a means of simplifying the interpretation of EEG and measuring recovery of EEG entropy [14]. IQ only evaluates the

information of the gross EEG without sub-band information, however. As shown in this experiment, EEG can be decomposed into different frequency sub-bands: gamma (above 30 Hz), beta (16–30 Hz), alpha (8–15 Hz), theta (4–8 Hz), and delta (below 4 Hz). The SIQ algorithm allows additional sub-band analysis to identify the most relevant sub-bands of EEG during brain recovery after CA.

The high frequency EEG signal classified into beta, and gamma frequency sub-bands are predominantly generated and synchronized by cortical mechanisms, whereas subcortical structures are responsible for the generation and synchronization of low-frequency delta-, theta- and alpha-band EEG [18]. In our SIQ EEG analysis, the best recovery was in the hypothermia group in all EEG frequency sub-bands. Therapeutic hypothermia has been recommended as an effective treatment of brain injury after CA [1, 19, 20] and has been validated to improve neurological recovery and reduce ischemic neuronal injury after CA [21–23], consistent with our results.

The present study, for the first time, confirmed our hypothesis that the gamma-band makes the greatest contribution to the prognostic value of SIQ after CA. Recovery of the gamma-band SIQ was a robust, early, and consistent electrophysiological marker of better functional recovery. The association between gamma-band SIQ and outcome was stronger than conventional SIQ. This result was not surprising because gamma frequencies are considered to be an indicator of engaged intracortical networks necessary for recovery of higher order neurological processes [24]. Gamma power increases with sensory stimulus [25–27], cognitive processing [28], and lexical processing [29], for example. In the cerebral cortex, gamma-band activity is increased during memory tasks, learning [30], and other advanced functional behaviors [31–33].

Significantly higher gamma-band SIQ was found in the hypothermia group than in the normothermia and hyperthermia groups. The most notable differences occurred within the first 2 hrs after ROSC when the rats remained unresponsive and neurological deficits may be obscured. Gamma-band SIQ was also strongly associated with 72-hr NDS as early as 30 mins after ROSC and was significantly higher in the good functional outcome group than the bad functional outcome group throughout the 72 hrs after ROSC. The optimal cut-off points were determined by constructing ROC curves for prediction of 72-hr functional outcome. For gamma-band SIQ, a value > 0.39 had exceptional sensitivity of 0.727 and specificity of 100% at 2-hr post-ROSC for prediction of good functional outcome. Similarly accurate cut-off points were also found at each time point from 1 hr to 3.5 hrs.

The mechanism of alterations of gamma-band activity after CA has not been fully elucidated. Gamma frequencies are generated and synchronized by the interaction of two neurotransmitters: gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter in the mammalian nervous system, and glutamate [34, 35]. Glutamate concentration is increased in the ischemic brain [36, 37], which may result in reduction of cerebral metabolism and energy consumption as a means of neuroprotection. This mechanism will prioritize energy usage for active glutamate removal to prevent excitotoxicity [38].

Hyperthermia further increases the concentration of glutamate [39], leading to excessive glutamate activity [40] and simultaneously decreases transmission of GABA [41], amplifying glutamate excitotoxicity. This mechanism may decrease high frequency EEG activity, resulting in the loss of the gamma-band in hyperthermic animals destined for poor functional recovery. Conversely, hypothermia reduces glutamate-mediated neuroexcitation and suppresses downstream secondary injuries induced by CA [20, 37, 42, 43]. In this study, hypothermia mainly improved recovery of high frequency rhythms, especially in the gamma-band, which was associated with better functional outcome after CA.

We also evaluated the prognostic value of delta-band EEG and found that the delta rhythm showed poor ability to predict neurologic outcome and was not as sensitive to the temperature intervention as other sub-bands. During global ischemia, high frequency EEG rhythms are quickly suppressed and lower frequencies predominate until the EEG signal is fully suppressed [44–46]. After ROSC, there is early recovery of the low-frequency EEG signal followed by higher frequencies [47]. During coma, low frequency EEG is produced by hyperpolarization of cortical neuronal membrane potentials with the absence of spontaneous synaptic potentials [48]. Our studies indicate that, after ROSC, waves of low frequency bands gradually return prior to emergence from coma. Because the delta frequency band predominates during coma, recovery of delta-band SIQ had little prognostic value. Therefore, the delta-band appears to be a constant component of EEG signal. These results confirmed our earlier findings that delta frequencies made little contribution to the prognostic value of conventional SIQ [15] or IQ [13, 14] after CA with post-resuscitation temperature management.

In this pre-clinical EEG study, SIQ values were normalized to the pre-arrest baseline. While this may be a limitation to clinical translation, we believe similar results could be obtained with a standardized baseline generated from control groups in the translation to clinical use. We evaluated neurological outcomes with the NDS, which is heavily weighted to basic motor functions and coordination rather than more complex tasks. Because gamma-band EEG frequencies are produced during higher cognitive processes, future studies will measure the association of gamma-band recovery with more complex behaviors, such as learning and memory, after CA. These studies will help to investigate the role of gamma activity in neurological recovery in CA survivors treated with targeted temperature management.

Conclusions

This study demonstrated that temperature management had significant effects on recovery of EEG activity in different sub-bands, especially in the gamma-band. The rate of recovery of gamma-band SIQ was strongly associated with functional outcomes. This association was detectable soon after ROSC and was consistent throughout the recovery period. If translated into clinical practice, these experiments may bring new insights into real-time bedside neuromonitoring and prognostication after CA. Because EEG can be readily obtained from humans and is part of the standard clinical assessment of CA survivors, the ultimate goal of the project is to develop an accurate bedside prognostic marker for neurological recovery based on gamma-band SIQ.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

The core temperature (mean±S.E.M.) was well controlled in all three temperature groups – hypothermia ($33\pm 1^{\circ}\text{C}$, blue), normothermia ($37\pm 0.5^{\circ}\text{C}$, green), and hyperthermia ($39\pm 0.5^{\circ}\text{C}$, red) – during the 6-hr temperature management period (highlighted).

Figure 2.

Sub-band information quantity (SIQ) plots from two representative rats with good outcome (NDS=80) and bad outcome (NDS=56). From top to bottom, the plots represent conventional SIQ and SIQ of the sub-bands from lowest to highest frequency. The most distinct difference in SIQ between these two rats was shown in the gamma band, including the period beyond 3 hours.

Figure 3.

The sub-band SIQ values in the three temperature groups at different time intervals. **A**, Conventional SIQ values of the hypothermia group were significantly higher than the other temperature groups from 30 mins to 2.5 hrs after ROSC. **B**, There were significant differences in gamma-band SIQ among the three groups at all time intervals (30 mins, 1 hr, 1.5 hrs, 2 hrs, 2.5 hrs, 3 hrs, 3.5 hrs, 24 hrs and 48 hrs). **C**, In the delta sub-band, a significant difference in SIQ values between the normothermia and hyperthermia groups was seen only at 4 hrs after ROSC. * $p < 0.05$, ** $p < 0.01$.

Figure 4.

Representative Pearson correlation (r value) plot between SIQ value and 72-hr NDS. The gamma-band SIQ most consistently correlated with 72-hr NDS from 30 mins until 72 hrs after ROSC among all sub-bands. As shown, the gamma-band SIQ at 3 hrs after ROSC had good correlation with 72-hr NDS (n=19, r value: 0.782, $p<0.01$).

Figure 5.

The comparison of SIQ-qEEG values (mean±S.E.M.) between the good functional outcome group (72-hr NDS ≥ 60) and bad functional outcome group (72-hr NDS < 60). **A**, Aggregate SIQ demonstrated significant differences, except in the delta-band, in conventional SIQ (good/bad: 0.80±0.02/0.65±0.02, p<0.01), theta (0.86±0.02/0.75±0.02, p<0.01), alpha (0.78±0.02/0.64±0.01, p<0.01), beta (0.69±0.02/0.51±0.01, p<0.01), and gamma (0.59±0.02/0.32±0.01, p<0.01). **B and C**, Significant differences in conventional SIQ and gamma-band SIQ between the outcome groups were shown continuously from 30 mins to 72 hrs after ROSC. **D**, The delta-band SIQ showed poor discrimination between the outcome groups at most time intervals. *p<0.05, **p<0.01.

Figure 6.

Receiver operation characteristic (ROC) curves were used to identify the optimal SIQ cut-off points with area under the ROC curve > 0.8 and highest specificity for good outcome. The cut-off point for gamma-band SIQ > 0.39 at 2 h after ROSC had a sensitivity of 0.727 and specificity of 1 with an area under ROC curve of 0.86 (shown).

Table 1

Aggregate SIQs from uninjured and CA rats (mean±S.E.M.) in temperature groups

Temperature	Hypothermia	Normothermia	Hyperthermia
EEG Rhythm			
Rats with No Injuries (N=4)			
Conventional SIQ	0.87±0.04	0.91±0.07	0.96±0.04
Delta-band	0.93±0.09	1.06±0.02	1.08±0.08
Theta-band	1.15±0.04	1.16±0.04	1.18±0.03
Alpha-band	1.06±0.09	1.01±0.11	1.13±0.07
Beta-band	0.83±0.08	0.85±0.09	0.92±0.09
Gamma-band	0.40±0.09	0.48±0.09	0.48±0.08
Rats with Cardiac Arrest (N=24)			
Conventional SIQ	0.80±0.02**	0.69±0.02 [†]	0.66±0.02 ^{§§}
Delta-band	1.06±0.02	1.08±0.03 [‡]	1.00±0.03 [§]
Theta-band	0.86±0.02**	0.76±0.02	0.77±0.03 ^{§§}
Alpha-band	0.79±0.02**	0.66±0.03	0.66±0.03 ^{§§}
Beta-band	0.70±0.02**	0.56±0.03	0.53±0.03 ^{§§}
Gamma-band	0.60±0.03**	0.40±0.03 [†]	0.34±0.03 ^{§§}

Hypothermia compared with normothermia,

*
p<0.05,**
p<0.01

Normothermia compared with hyperthermia,

[†]
p<0.05,[‡]
p<0.01

Hypothermia compared with hyperthermia,

[§]
p<0.05,^{§§}
p<0.01

Table 2

The prognostic values of SIQ-qEEG markers

	30 mins	1 hr	1.5 hrs	2 hrs	2.5 hrs	3 hrs	3.5 hrs	4 hrs	24 hrs	48 hrs	72 hrs
N of survivors	24	24	24	24	24	23	23	22	21	20	19
The correlation coefficients between SIQ values and 72-hr NDS scores											
Conventional SIQ	0.657**	0.750**	0.686**	0.669**	0.640**	0.646**	0.550*	0.437	0.643**	0.587**	0.656**
Delta-band	0.196	0.154	0.294	0.007	-0.165	-0.187	-0.006	0.053	-0.049	-0.137	-0.139
Theta-band	0.648**	0.703**	0.664**	0.608**	0.472*	0.295	0.116	-0.041	0.471*	0.395	0.509*
Alpha-band	0.710**	0.787**	0.739**	0.729**	0.646**	0.501*	0.272	0.168	0.414	0.457*	0.589*
Beta-band	0.696**	0.772**	0.699**	0.672**	0.649**	0.601**	0.420	0.272	0.529*	0.504*	0.626**
Gamma-band	0.555*	0.599**	0.520*	0.649**	0.712**	0.782**	0.788**	0.667**	0.788**	0.655**	0.726**
The correlation coefficients between good electrophysiological outcome and good functional outcome											
Conventional SIQ	0.367	0.832**	0.330	0.585**	0.608**	0.497*	0.510*	0.510*	0.678**	0.678**	0.489*
Delta-band	0.194	0.251	0.084	-0.161	-0.161	-0.071	0.007	0.007	0.071	0.084	0.214
Theta-band	0.540**	0.678**	0.324	0.678**	0.438*	0.251	0.269	0.084	0.585**	0.678**	0.489*
Alpha-band	0.438*	0.678**	0.151	0.678**	0.753**	0.497*	0.175	0.329	0.497*	0.497*	0.555**
Beta-band	0.438*	0.749**	0.151	0.585**	0.608**	0.585**	0.438*	0.418*	0.497*	0.497*	0.555**
Gamma-band	0.497*	0.669**	0.486*	0.664**	0.749**	0.678**	0.678**	0.678**	0.678**	0.585**	0.592**
SIQ cut-off points (sensitivity) with highest specificity (100%) and area under ROC curve >0.8											
Conventional SIQ	0.66 (0.273)	0.67 (0.909)	0.73 (0.818)	0.80 (0.727)	0.87 (0.545)	0.93 (0.182)	0.88 (0.364)	None	1.10 (0.091)	1.02 (0.364)	0.96 (0.700)
Delta-band	None	None	None	None	None	None	None	None	None	None	None
Theta-band	0.80 (0.273)	0.90 (0.545)	0.95 (0.273)	0.96 (0.455)	2.03 (0)	None	None	None	None	None	None
Alpha-band	0.65 (0.364)	0.71 (0.818)	0.76 (0.909)	0.81 (0.727)	0.85 (0.727)	None	None	None	None	None	None
Beta-band	0.47 (0.455)	0.52 (0.818)	0.58 (0.818)	0.70 (0.545)	0.86 (0.364)	0.94 (0.182)	None	None	None	None	0.95 (0.400)
Gamma-band	0.24 (0.273)	0.32 (0.636)	0.35 (0.636)	0.39 (0.727)	0.55 (0.545)	0.68 (0.455)	0.61 (0.545)	0.73 (0.273)	1.11 (0.182)	0.98 (0.455)	1.00 (0.600)

*
p<0.05,**
p<0.01

None: There were no cut-off points with the area under ROC curve >0.8