Early electrophysiologic markers predict functional outcome associated with temperature manipulation after cardiac arrest in rats

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Objective: **Therapeutic hypothermia after cardiac arrest improves survival and functional outcomes, whereas hyperthermia is harmful. The optimal method of tracking the effect of temperature on neurologic recovery after cardiac arrest has not been elucidated. We studied the recovery of cortical electrical function by quantitative electroencephalography after 7-min asphyxial cardiac arrest, using information quantity (IQ).**

Design: **Laboratory investigation.**

Setting: **University medical school and animal research facility.**

Subjects: **A total of 28 male Wistar rats.**

Interventions: **Using an asphyxial cardiac arrest rodent model, we tracked quantitative electroencephalography of 6-hr immediate postresuscitation hypothermia (at 33°C), normothermia (37°C), or hyperthermia (39°C) (n = 8 per group). Neurologic recovery was evaluated using the Neurologic Deficit Score. Four rats were included as a sham control group.**

Measurements and Main Results: **Greater recovery of IQ was found in rats treated with hypothermia (IQ = 0.74), compared with normothermia (IQ = 0.60) and hyperthermia (IQ = 0.56) ($p < .001$). Analysis at different intervals demonstrated a significant separation of IQ scores among the temperature groups within the first 2 hrs postresuscitation ($p < .01$). IQ values of >0.523 at 60 mins postresuscitation predicted good neurologic outcome (72-hr Neurologic Deficit Score of ≥60), with a specificity of 100% and sensitivity of 81.8%. IQ was also significantly lower in rats that died prematurely compared with survivors ($p < .001$). IQ values correlated strongly with 72-hr Neurologic Deficit Score as early as 30 mins post–cardiac arrest (Pearson's correlation 0.735, $p < .01$) and maintained a significant association throughout the 72-hr experiment. No IQ difference was noted in sham rats with temperature manipulation.**

Conclusions: **The enhanced recovery provided by hypothermia and the detrimental effect by hyperthermia were robustly detected by early quantitative electroencephalographic markers. IQ values during the first 2 hrs after cardiac arrest accurately predicted neurologic outcome at 72 hrs. (Crit Care Med 2008; 36:1909–1916)**

KEY WORDS: cardiac arrest; hypothermia; hyperthermia; electrophysiology; functional outcome; ischemia

Approximately 164,600 cardiac arrests (CAs) occur in the United States each year (1). Among initial survivors, 80% remain comatose after resuscitation (2), and neurologic complications represent the leading cause of disability (3, 4). The ischemic brain is sensitive to temperature, such that small differences can critically influence neuropathological outcomes (5). Hyperthermia has been demonstrated to worsen ischemic outcome and is associated with increased brain injury in animal models (5, 6) and clinical studies (7–9). On the other hand, induced hypothermia to 32–34°C is recommended for comatose survivors of CA (10, 11) and was recently shown to significantly mitigate brain injury in animal models (12–14) and clinical trials (15–18).

Neurologic monitoring of comatose CA survivors is complicated by the requirement for sedative and paralytic agents, particularly in patients who are treated with hypothermia. Comatose CA survivors are typically cared for by nurses and physicians in general or cardiac intensive care units with little specialized training in neurologic examination. In addition, the ability to detect even major changes in brain function in comatose patients is limited. Electroencephalography (EEG) is frequently employed for neuromonitoring and prognostication (19–21). A recent publication from our group demonstrated that physicians were more likely to withdraw supportive measures in patients with negative neurologic predictors (22). As a diagnostic tool, however, waveform-based EEG analysis is subjective and laborious, with results depending on the interpreter's expertise (23). Previous attempts to use early quantitative EEG (qEEG) as a measure of neurologic recovery after CA have utilized power spectral analysis (24). A readily

***See also p. 1983.**

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translatable tool for tracking the effect of temperature on recovery of cortical electrical function has not been thoroughly elucidated.

We have previously established and validated a rodent model for global ischemic brain injury after CA (25, 26) using a standardized Neurologic Deficit Score (NDS) that was adapted from human and animal scales (12, 14, 17, 27–29). We developed the theoretical measure information quantity (IQ) to provide an objective measure of entropy in EEG amplitude (30). Our subsequent work showed that greater injury was associated with lower entropy and reduced IQ values. This methodology tracked functional outcome (23, 25, 26, 31–35) and accurately differentiated EEG recovery between rats treated with hypothermia and normothermia after CA (23, 33). To expand on these findings, we evaluated the impact of the qEEG-IQ marker in monitoring the effect of temperature on neurologic recovery.

MATERIALS AND METHODS

A total of 24 adult male Wistar rats (300–350 g, Charles River, Wilmington, MA) were randomly assigned to 7-min asphyxial CA and resuscitation with either hypothermia (hypothermia group), normothermia (normothermia group), or hyperthermia (hyperthermia group) (n = 8 per group). Another four anesthetized rats were included as a sham control group for evaluation of the effect of temperature on qEEG in the absence of CA injury. The experimental protocol was approved by the Johns Hopkins Animal Care and Use Committee.

Experimental Asphyxia–Cardiac Arrest Model. The asphyxial CA and cardiopulmonary resuscitation model used previously validated protocols (23, 26, 30, 36). In brief (details described by Jia et al. [23]), rats were mechanically ventilated with 1.0% halothane in N_2/O_2 (50%/50%). The femoral artery and vein were cannulated to monitor mean arterial pressure, sample arterial blood gases, and administer fluid and drugs. Five minutes of baseline recording with halothane was followed by a 5-min washout to ensure no significant residual effect of halothane on qEEG (25). CA was initiated via asphyxia with paralysis and cessation of mechanical ventilation for 7 mins. Cardiopulmonary resuscitation was performed with sternal compressions (200/min) until return of spontaneous circulation (ROSC). Arterial blood gases were obtained four times per animal: at baseline and at 10, 20, and 40 mins after resuscitation. Sedative agents were not used after CA to avoid confounding influences on EEG (37).

Immediate Temperature Manipulation After Cardiac Arrest. An intraperitoneal sensor (G2 E-mitter 870-0010-01, Mini Mitter, Sun River, OR) implanted 1 wk before experiments was used to monitor core temperature (23). Hypothermia or hyperthermia was induced immediately after ROSC. Hypothermia was achieved through surface cooling with misted water to achieve the target temperature of 33°C within 15 mins (23, 30). The core temperature was maintained between 32°C and 34°C for 6 hrs. Rats were then gradually warmed from 33.0°C to 37.0°C in the course of 2 hrs.

Hyperthermia was achieved using a warming blanket and an automatic warming lamp (Thermalet TH-5, model 6333, Physitemp Instruments, Clifton, NJ) to achieve a target temperature of 39°C within 15 mins, and this temperature was maintained at 38.5–39.5°C for 6 hrs. Rats were then passively cooled to 37.0°C in the course of 2 hrs.

The normothermia group was maintained at 36.5–37.5°C for 8 hrs after ROSC. To ensure that no temperature fluctuation occurred after the resuscitation, such as spontaneous hypothermia (6), all animals were then kept inside a neonatal incubator (Isolette infant incubator model C-86, Air-Shields, Hatboro, PA) for the first 24 hrs post-ROSC.

For the purpose of comparing the direct effect of temperature on IQ, we collected EEGs in four sham animals. Sham rats underwent identical surgical preparation without CA. Anesthesia was maintained with 1.0% halothane in N_2/O_2 (50%/50%) throughout the experiment. Continuous EEG was recorded. Four rats were monitored during normothermic baseline for 30 mins, then a target temperature of 32–34°C was maintained for 1 hr. During the course of 30 mins, the rats were allowed to return to normothermia (36.5–37.5°C). After 30 mins, a temperature of 38.5–39.5°C was maintained for 1 hr.

EEG Recording and Quantitative EEG Analysis. EEG signals were recorded from both hemispheres at a sampling rate of 250 Hz (23). Serial 30-min EEG recordings were then performed at 24, 48, and 72 hrs after ROSC in each group. Signals were examined for noise, both in time domain using WinDaq software (Dataq Instruments, Akron, OH) and in frequency spectrum using MATLAB (MathWorks, Natick, MA). Signals that were contaminated by artifact were not included in the final analysis.

We determined the amount of information in the EEG using our previously reported IQ algorithm. First, the EEG waveform was divided into a series of windows of equal length. For the EEG signal in each window, wavelet coefficients were computed using a discrete wavelet transform. The statistical distribution of the wavelet coefficients within a window was then determined by constructing a histogram. Using the frequency of wavelet coefficients in each bin of the histogram, the information or disorder was calculated using the formula for entropy. The final value of the entropy of wavelet coefficients for a single window of EEG is called the *information quantity*. To quantify how entropy evolves over time, IQ was averaged over several intervals. To compare IQ among multiple rats, the IQ time averages were normalized to a baseline mean, which is the average IQ for the time window preceding CA.

Table 1. Neurodeficit scoring for rats (Best function = 80; Worst function = 0)

A) General behavioral deficit	Total score: 19
Consciousness	Normal 10/Stuporous 5/Comatose or unresponsive 0
Arousal:	Eyes open spontaneously 3/Eyes open to pain 1/No Eye Opening 0
Respiration:	Normal 6/Abnormal (hypo- or hyperventilation) 3/Absent 0
B) Brain-stem function:	Total score: 21
Olfaction: response to smell of food	Present 3/Absent 0
Vision: head movement to light	Present 3/Absent 0
Pupillary reflex: pupillary light reflex	Present 3/Absent 0
Corneal reflex:	Present 3/Absent 0
Startle reflex:	Present 3/Absent 0
Whisker stimulation:	Present 3/Absent 0
Swallowing: swallowing liquids or solids	Present 3/Absent 0
C) Motor assessment: strength:	Normal 3/Stiff or Weak 1/No movement/Paralyzed 0
Total score: 6	Left and Right side tested and scored separately
D) Sensory assessment: pain:	Brisk Withdrawal with pain 3/Weak or abnormal response (extension or flexion posture) 1/No Withdrawal 0
Total score: 6	Left and Right side tested and scored separately
E) Motor behavior:	Total score: 6
Gait coordination:	Normal 3/Abnormal 1/Absent 0
Balance on beam:	Normal 3/Abnormal 1/Absent 0
F) Behavior:	Total score: 12
Righting reflex:	Normal 3/Abnormal 1/Absent 0
Negative geotaxis:	Normal 3/Abnormal 1/Absent 0
Visual placing:	Normal 3/Abnormal 1/Absent 0
Turning alley:	Normal 3/Abnormal 1/Absent 0
G) Seizures (convulsive or non-convulsive):	No Seizure 10/Focal Seizure 5/General Seizure 0
Total score: 10	

As a result of this analysis, which has been described previously (23, 30), we obtained normalized EEG values that range from 1.0 (control) to 0.0 (isoelectricity). IQ is normalized to baseline values, such that higher values reflect greater EEG entropy relative to baseline. We selected eight segments in each rat and calculated IQ values: baseline (IQ1) and 30 mins (IQ2), 1 hr (IQ3), 2 hrs (IQ4), 4 hrs (IQ5), 24 hrs (IQ6), 48 hrs (IQ7), and 72 hrs (IQ8) post-ROSC.

Neurologic Evaluation. NDS was determined after the recovery period on the first day and then repeated at 24, 48, and 72 hrs after ROSC. The NDS measures level of arousal, cranial nerve reflexes, motor function, and simple behavioral responses and has a range of 0–80 (Table 1) (23, 26). The NDS examination was performed by a trained examiner blinded to temperature group, and the primary outcome measure of this experiment was defined as the 72-hr NDS score. We prespecified the NDS cut-off for good (NDS ≥60) and poor (NDS <60) outcome (26, 31), which represents a level of neurologic function required for independent function.

Statistical Methods. Statistical analysis was performed using a computerized statistical package (Statistics Program for the Social Sciences version 14, SPSS, Chicago, IL). Group values that were parametric were reported as mean ± SEM, and nonparametric variables were reported as median (interquartile range). Univariate analysis was performed for parametric data with Student's *t*-test for continuous variables, chi-square for categorical variables, and least significant difference for multiple comparisons. The multivariate general linear model was used for comparison of aggregate data to account for influencing factors, such as temperature. Nonparametric analysis of variance was used to test for differences in rank order NDS as a repeated measure. The mortality rate was analyzed by Fisher's exact test (crosstabs), and survival was analyzed by a Kaplan-Meier test. Pearson's correlation of bivariate analysis was used to analyze the correlation between 72-hr NDS score with serial IQ. A receiver operating characteristic curve was constructed to determine the IQ cutpoint with optimal sensitivity and specificity for good neurologic outcome (72-hr NDS of ≥60). A level of $p < .05$ was selected to consider differences significant.

RESULTS

Temperature and Arterial Blood Gas Monitoring

The target temperature was readily achieved and maintained for the defined duration for each of the three groups, as shown in Figure 1. Arterial blood gas data, including arterial pH, HCO_3^-, Pco_2, Po_2, and oxygen saturation in hypothermic, normothermic, and hyperthermic groups, were similar (Table 2).

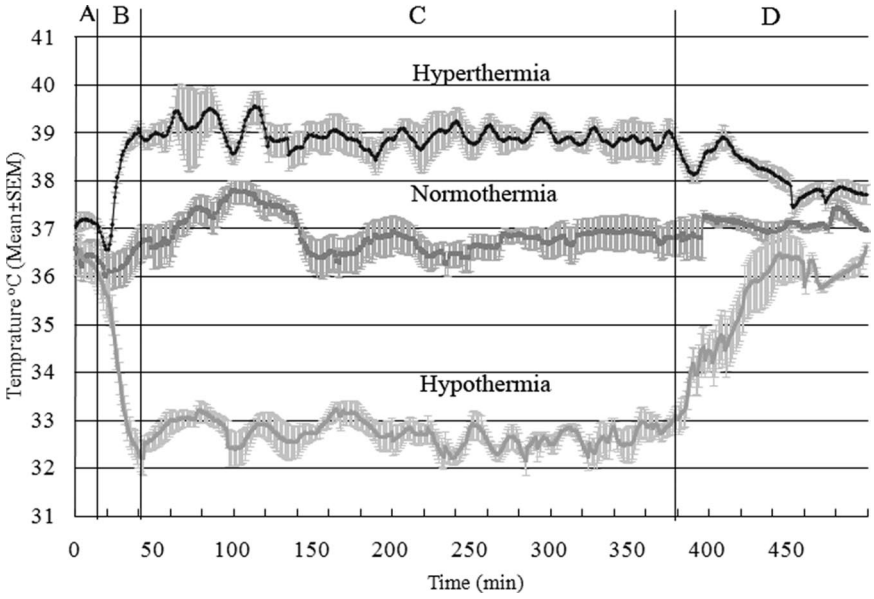

Figure 1. Temperature recording of rats subjected to 7 mins of asphyxial cardiac arrest. These different cohorts received hyperthermia (*upper*), normothermia (*middle*), and hypothermia (*bottom*). The plots show temperatures during four different phases of the experiment. *A*, baseline and asphyxial cardiac arrest period, with cardiopulmonary resuscitation at 17 mins; *B*, temperature manipulation induction period; *C*, temperature manipulation maintenance period; *D*, temperature manipulation recovery period. The *solid black line* is mean temperature and *gray field* is SEM.

Table 2. Arterial blood gas data in cardiac arrest experiment among three groups

	Hypothermia	Normothermia	Hyperthermia	*p* Value
Baseline				
pH	7.42 ± .02	7.43 ± 0	7.44 ± .01	.79
Pco_2 (mmHg)	39 ± 4	37 ± 1	33 ± 2	.61
Po_2 (mmHg)	383 ± 25	342 ± 41	362 ± 37	.71
HCO_3 (mmol/L)	24 ± 5	24 ± 1	22 ± 1	.54
O_2SAT (%)	100 ± 0	100 ± 0	100 ± 0	1.00
10 mins postresuscitation				
pH	7.35 ± .02	7.35 ± .04	7.36 ± .02	.52
Pco_2 (mmHg)	36 ± 2	37 ± 2	35 ± 1	.48
Po_2 (mmHg)	403 ± 52	496 ± 19	449 ± 46	.13
HCO_3 (mmol/L)	19 ± 1	20 ± 2	19 ± 1	.32
O_2SAT (%)	100 ± 0	100 ± 0	100 ± 0	.44
20 mins postresuscitation				
pH	7.37 ± .01	7.34 ± .03	7.39 ± .02	.06
Pco_2 (mmHg)	35 ± 2	41 ± 2	34 ± 2	.04[a]
Po_2 (mmHg)	496 ± 19	442 ± 36	494 ± 29	.36
HCO_3 (mmol/L)	20 ± 1	22 ± 1	20 ± 2	.61
O_2SAT (%)	100 ± 0	100 ± 0	100 ± 0	1.00
40 mins postresuscitation				
pH	7.31 ± .02	7.37 ± .01	7.41 ± .02	.30
Pco_2 (mmHg)	44 ± 4	41 ± 2	36 ± 3	.51
Po_2 (mmHg)	455 ± 39	462 ± 44	470 ± 22	.37
HCO_3 (mmol/L)	22 ± 1	23 ± 1	22 ± 1	.58
O_2SAT (%)	100 ± 0	100 ± 0	100 ± 0	1.00

[a]Statistically significant difference was noted but was minimal to cause any significant change in pH.

Functional Outcome, Survival Rates, and Mean Survival Duration

During the 72-hr experiment, aggregate analysis of NDS in all animals showed significant differences ($p < .001$) among the three groups. The hypothermia group consistently had better recovery, with higher NDS scores (median [interquartile range], 74 [61–74]) compared with the normothermia group (49 [47–61]) ($p < .001$), which was significantly higher at all time periods than the hyper-

thermia group (43 [0–50]) ($p = .001$) (Fig. 2*A*). There were significantly more good outcomes (NDS ≥60) among hypothermia rats (eight of eight) than the hyperthermia (zero of eight) ($p < .001$) and normothermia (three of eight) groups ($p = .026$), whereas no significant differences existed between the normothermia and hyperthermia groups.

Kaplan-Meier analysis demonstrated improved survival and mean duration of survival hours (both $p < .05$) in rats treated with hypothermia (eight of eight, 100%, 72 hrs) compared with the hyperthermia group (four of eight, 50%, 45 hrs), whereas the differences between the normothermia (seven of eight, 87.5%, 68 hrs) and other groups were nonsignificant (Fig. 2*B*).

Electrophysiologic Monitoring

Conventional EEG Assessment and qEEG Analysis. Within seconds of CA, EEG became isoelectric. Recovery was marked by several typical waveforms patterns, resembling burst-suppression, of variable duration. Using cursory subjective visual review alone, differences in raw EEG tracings (Fig. 3*A*) were not readily discernible among groups. Using IQ (Fig. 3*B*), differences among temperature groups were made apparent.

qEEG Markers Track Functional Recovery After Cardiac Arrest. Among four sham rats that did not undergo CA, no significant difference was observed in IQ values during the periods of hypothermia (0.59 ± 0.02, mean ± SEM), normothermia (0.60 ± 0.02), and hyperthermia (0.55 ± 0.04) ($p = .932$) (Fig. 4*A*). Unnormalized IQ values showed no significant differences between baseline recordings with halothane anesthesia (.60 ± .01) and the washout period (.61 ± .01) ($p = .589$), suggesting minimal effects of halothane on IQ.

Aggregate analysis of IQ showed significant differences ($p < .001$) among the three groups. Greater recovery of IQ was found in rats treated with hypothermia (.74 ± .03) compared with normothermia (.60 ± .03) ($p < .001$) and in those treated with normothermia over hyperthermia (.56 ± .03) ($p = .016$) (Fig. 4*B*).

Early qEEG Markers Tracked Functional Recovery with Temperature Manipulation. There was a significant separation of IQ scores among the three groups within the first 2 hrs after ROSC ($p < .01$) (Fig. 5*A*). Bivariate analyses revealed significant correlations between the 72-hr NDS and IQ values at 30 mins (Pearson's correlation, .735; $p < .01$), 1 hr (Pearson's correlation, .746; $p < .01$), 2 hrs (Pearson's correlation, .746; $p < .01$), 4 hrs (Pearson's correlation, .686; $p < .01$), 24 hrs (Pearson's correlation, .540; $p < .05$), 48 hrs (Pearson's correlation, .577; $p < .01$), and 72 hrs (Pearson's correlation, .639; $p < .01$) postresuscitation. The IQ value correlated well with the 72-hr NDS as early as 30 mins after ROSC (Fig. 5*B*).

qEEG Markers Predict Survival. Compared with survivors, rats that died prematurely had lower aggregate IQ values (dead/survivors: 0.48 ± 0.04/0.66 ± 0.02, $p < .001$) (Fig. 6*A*). Because a majority (three of five) of rats died within 4 hrs of ROSC, we calculated IQ every 30 mins, starting from 30 mins post-ROSC, up until 4 hrs. Rats that died prematurely showed significantly lower IQ during each 30-min interval (0.19 ± 0, 0.25 ± 0.04, 0.29 ± 0.04, 0.27 ± 0.06, 0.32 ± 0.04, 0.35 ± 0.06, 0.41 ± 0.06, and 0.43 ± 0.07, respectively) compared with an average of the first 4 hrs (0.60 ± 0.02) for survivors ($p < .05$) (Fig. 6*B*).

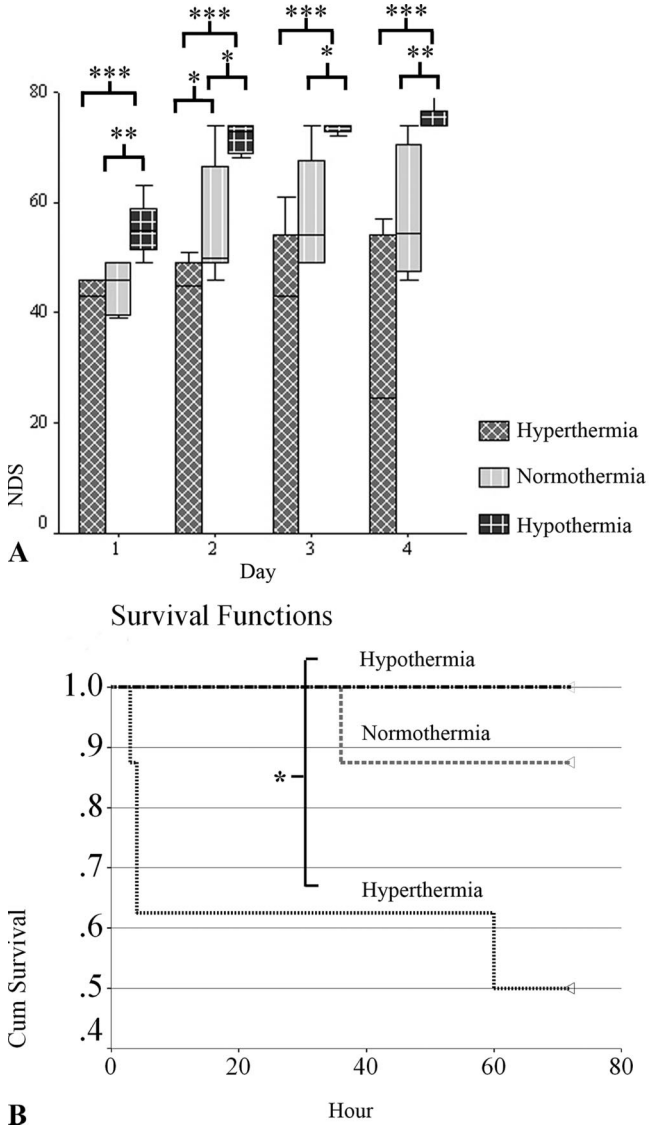

Figure 2. Outcomes by temperature manipulation groups measured by Neurologic Deficit Score (*NDS*; median [interquartile range]) (*A*) and survival (*B*). A significant difference in NDS was noted during the 72-hr experiment after asphyxial cardiac arrest (*CA*) between hypothermia and normothermia ($p < .001$) and between normothermia and hyperthermia ($p = .001$) groups. Significant differences existed in all periods between hypothermia and normothermia and at 2 days post-CA between normothermia and hyperthermia groups. The hypothermia group had a better survival rate and mean survival duration than the hyperthermia group. *$p < .05$; **$p < .01$; ***$p < .001$.

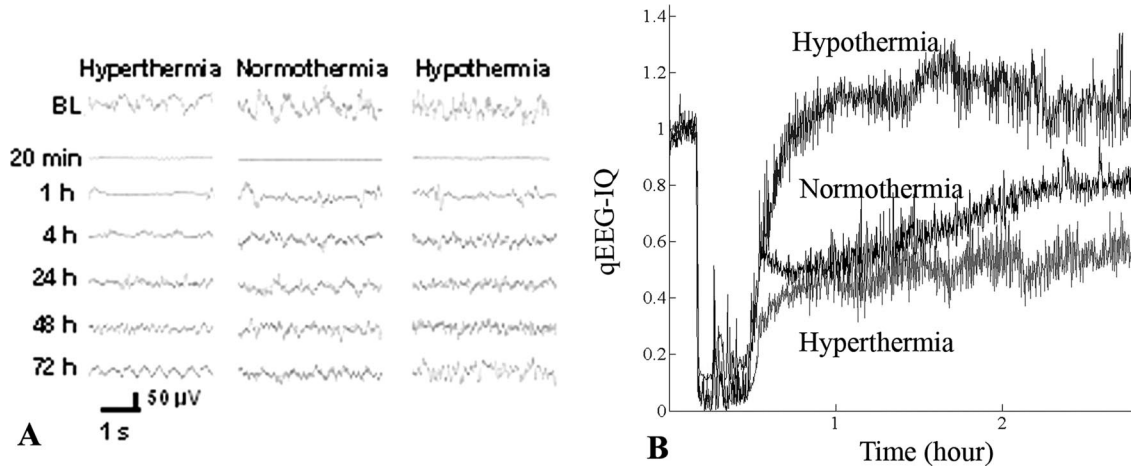

Figure 3. Raw electroencephalography (*EEG*) (*A*) and information quantity (*IQ*) (*B*) in the representative rats by temperature manipulation after cardiac arrest injury. The effect of temperature manipulation on the EEG signal recovery was not evident with conventional EEG assessment, whereas quantitative EEG analysis with IQ showed apparent differences during the recovery phase relative to baseline among temperature groups.

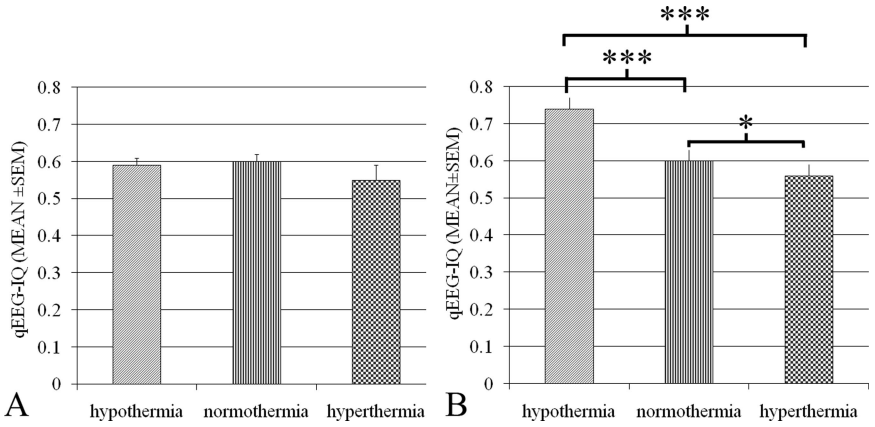

Figure 4. Quantitative electroencephalographic (*EEG*) information quantity (*IQ*) of animals with temperature manipulation in sham control (*A*) and 7-min cardiac arrest group (*B*). No significant difference existed in IQ in sham rats between the periods of hypothermia, normothermia, and hyperthermia ($p = .932$). Greater recovery of IQ was found in rats treated with hypothermia compared with normothermia, and higher IQ was found in normothermia over hyperthermia rats after return of spontaneous circulation (*ROSC*). *$p < .05$; **$p < .01$; ***$p < .001$.

qEEG Markers Predict Functional Outcome. Rats with bad functional outcomes (NDS <60) had significantly lower aggregate IQ values than those with good functional outcomes (NDS ≥60) (bad/good: 0.56 ± 0.02/0.73 ± 0.02, $p < .001$). Significant IQ differences were noted between animals with bad and good outcomes beginning at 30 mins after ROSC (bad/good: 0.35 ± 0.03/0.52 ± 0.03, $p < .001$) and at 1 hr (0.43 ± 0.02/0.66 ± 0.05, $p < .001$), 2 hrs (0.53 ± 0.02/0.73 ± 0.04, $p < .001$), 4 hrs (0.68 ± 0.02/0.79 ± 0.03, $p = .003$), 48 hrs (0.81 ± 0.05/0.98 ± 0.05, $p = .019$), and 72 hrs (0.79 ± 0.07/0.95 ± 0.04, $p = .048$) (Fig. 6*C*). Mean IQ scores were significantly correlated with good outcome at 30 mins (mean IQ, .43; Pearson's correlation, .685; two-sided, $p < .01$), 1 hr (mean IQ, .54; Pearson's correlation, .809; two-sided, $p < .01$), 2 hrs (mean IQ, .62; Pearson's correlation, .685; two-sided, $p < .01$), and 4 hrs (mean IQ, .73; Pearson's correlation, .511; two-sided, $p < .05$).

Receiver operating characteristic curves were constructed to determine IQ cutpoints at various intervals with optimal sensitivity and specificity for good neurologic outcome. Using this methodology, accurate cutpoints could be determined with areas under the receiver operating characteristic curve of >.80 at 30 mins, 60 mins, 2 hrs, and 4 hrs after ROSC. The most accurate cutpoint occurred at 60 mins post-ROSC, where an IQ value of >.523 had 81.8% sensitivity and 100% specificity for good outcomes with an area under the receiver operating characteristic curve of .864 (Fig. 6*D*).

DISCUSSION

Our experiment demonstrates that the entropy measure IQ is an early marker of injury and neurologic recovery after asphyxial CA. IQ accurately predicted the effect of temperature on recovery of cortical electrical activity, good/bad functional outcomes, and mortality soon after resuscitation.

This study further validated that IQ can accurately predict 72-hr NDS as early as 30 mins post-ROSC. The most significant differences occurred within the first 2 hrs, when rats were unresponsive and clinical evaluation is least reliable. A receiver operating characteristic curve was constructed to determine the optimal IQ cutpoint to predict good neurologic outcomes at 72 hrs. Good outcomes were predefined as a 72-hr NDS of >60 based on previous experience showing that those animals with scores of >60 were capable of functional independence. An IQ value of >0.523 at 60 mins from ROSC had excellent sensitivity and specificity for good outcomes. Cutpoints with similar predictive accuracy could be determined for IQ values at 2 and 4 hrs, as well. These data demonstrate that IQ thresholds can be determined as early as 60 mins after ROSC that reliably predict neurologic outcomes. If similar cutpoints can be determined in human studies, this technology may greatly enhance the predictive value of early EEG after CA.

EEG is a specific indicator of poor neurologic outcome in comatose survi-

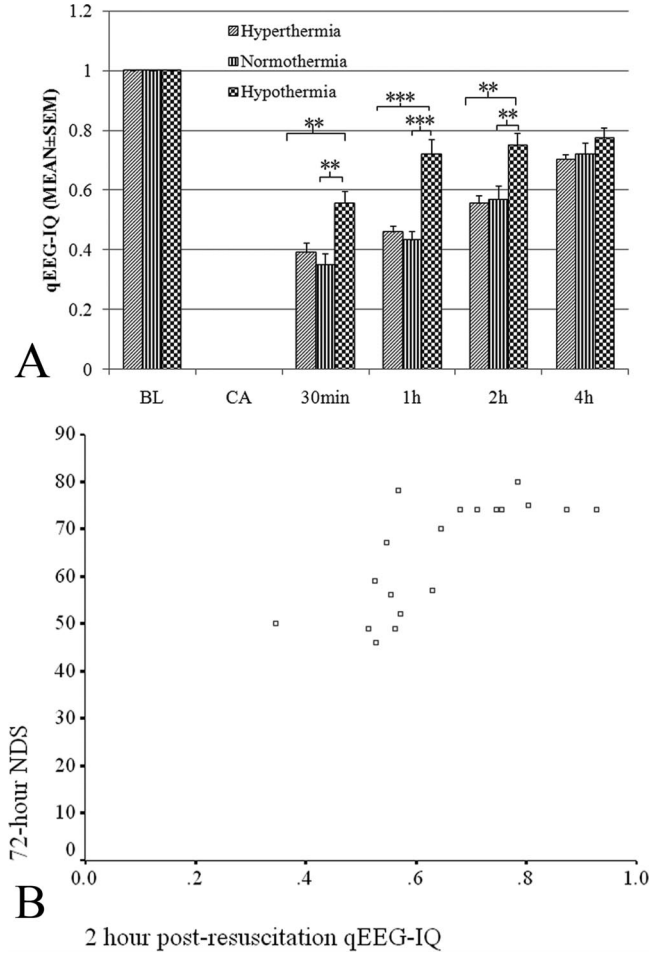

Figure 5. Comparison of quantitative electroencephalographic (*qEEG*)–information quantity (*IQ*) at different intervals by temperature groups (*A*) and correlation between 2-hr qEEG-IQ and 72-hr Neurologic Deficit Score (*NDS*) (*B*). $*p < .05$; $**p < .01$; $***p < .001$. Aggregate comparisons show that IQ was significantly different among hypothermia (.74 ± .03), normothermia (0.60 ± 0.03), and hyperthermia (.56 ± .03) groups ($p < .001$). IQ values correlated well with 72-hr NDS at 2 hrs after cardiac arrest (*B*).

vors of CA when characteristic changes occur (19–21, 38). Whereas the manual determination of continuous EEG is laborious, subjective, and requires specialized knowledge, persistence of burst-suppression can be readily monitored with the help of entropy-based EEG analysis. From a neuromonitoring perspective, this study highlights the importance of the immediate postresuscitation period when brain injury may be most amenable to therapeutic interventions (39). The rapid detection of brain response by qEEG during the first 2 hrs postresuscitation points to the importance of this period in the effort to protect the brain. Given that one of the primary goals is to improve functional outcome, we have to create a paradigm shift to include detection and management of brain injury in the first 2 hrs. As a continuous, noninvasive strategy, qEEG may also allow physicians to monitor the response to potential neuroprotective strategies by translating complicated and subjective waveform analysis into an objective measure. If the same relationship is seen in humans, changes in EEG entropy after CA may be helpful as a real-time monitor of recovery and to tailor therapies such as hypothermia.

With the use of sham animals, we also demonstrated that it is not the temperature itself that alters EEG but the response of the injured brain to hypothermia or hyperthermia as manifested in the qEEG. The temperature manipulation in these experiments was patterned after clinical trials (15, 18) that utilized external cooling and extracerebral temperature monitoring. In addition, previous animal studies have shown that the thermal curves are similar in the brain and peritoneum, independent of the thermal state (40), and most studies have shown that differences in brain and core body temperature are not significant (41). As a translational experiment, we chose this methodology because brain temperature monitoring and invasive cooling are uncommon in clinical practice.

Previous animal studies of induced hyperthermia at 40°C (5, 6) to 42.0°C (42, 43) led to poor outcomes, and human studies showed adverse outcomes with temperatures between 38.3°C and 39°C (8, 9, 44). In this study, we chose the target temperature of mild hyperthermia as 39°C to simulate clinical hyperthermia. Our results did not show a significant difference in early IQ and NDS between the hyperthermia and normothermia groups likely, due to a low target temperature range (38.5–39.5°C). The lack of difference between these groups, however, was consistent in IQ and NDS, which lends reassurance that the early IQ values are an accurate predictor of recovery.

Absence of histopathological data is a potential limitation of this study. Although we have previously demonstrated that histopathological markers for ischemic cell death correlate with qEEG and NDS measures (26, 37, 45), we also acknowledge that postmortem histologic markers in rats have been a poor indicator of clinical significance in human trials of the same agents and have been less predictive than early behavioral assessments (46–48). As such, we put more emphasis on functional outcome and real-time biological measures of recovery (qEEG) as a means to clinical translation.

In this EEG analysis, we used an IQ measure that relies on relative entropy compared with baseline. Although we recognize this as a limitation, we anticipate that similar results will be produced using standardized normal controls as a baseline. We acknowledge that the use of sedatives in clinical practice may affect EEG in ways that were not addressed in this experiment (49, 50); however, sedatives have shown equivocal effects on EEG in other studies (51–53). Our laboratory results have also shown that halothane did not have a significant effect on IQ using this particular animal model (25, 35). Because the predictive effect of IQ is most robust in the first few hours and sedation is rarely required during this period due to coma, we are optimistic that sedatives will have minimal effect on the translation of this technology. To

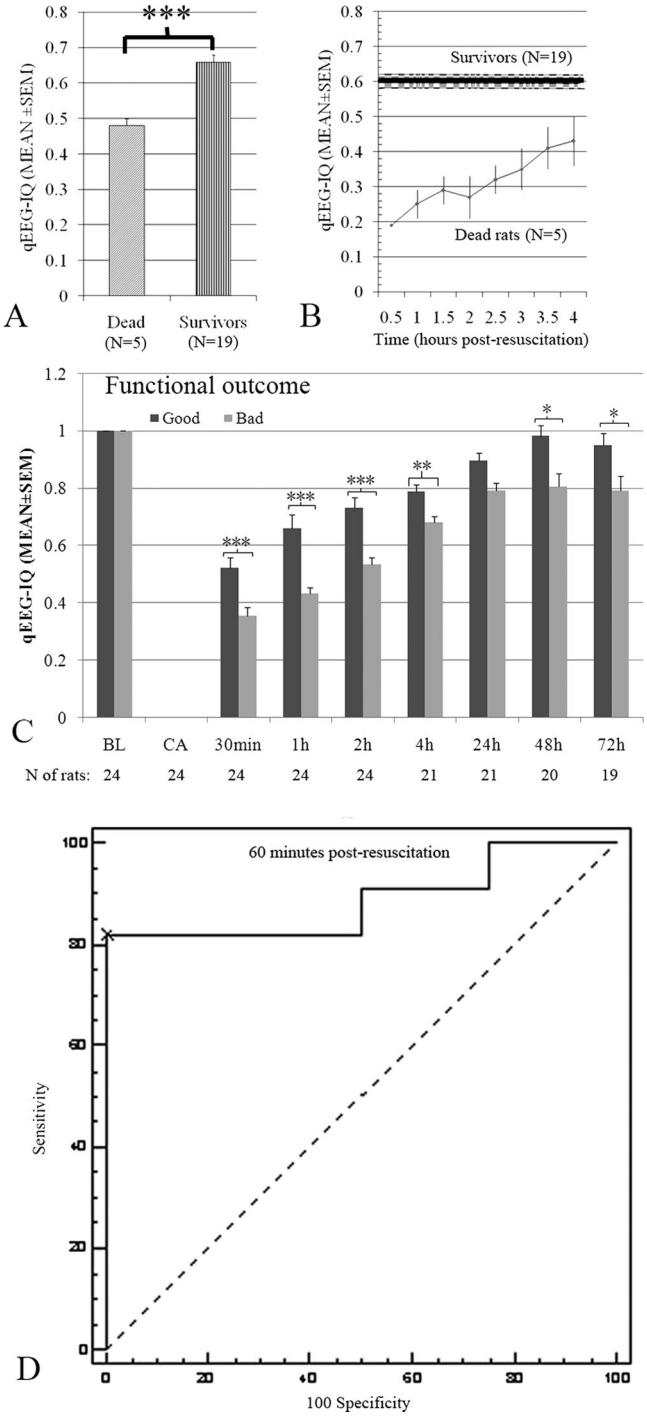

Figure 6. Comparison of quantitative electroencephalographic (*qEEG*)–information quantity (*IQ*) at different intervals by survival in all animals (*A*), first 4-hr postresuscitation intervals (*B*), by functional outcome (*C*), and 1-hr postresuscitation receiver operating characteristics (*ROC*) curve demonstrating the IQ value with optimal sensitivity and specificity for good neurologic outcomes (*D*). $*p < .05$; $**p < .01$; $***p < .001$. Rats that died within 72 hrs postresuscitation had lower IQ values during the 72-hr experiment than survivors. Rats that died prematurely showed significantly lower IQ during each 30-min interval compared with an average of the first 4 hrs (0.60 ± 0.02, *black line* is mean and *shadow* is SEM in *B*) for survivors ($p < .05$). Rats with a bad functional outcome (Neurologic Deficit Score [*NDS*] of <60) had significantly lower qEEG-IQ values in the course of 72 hrs than those with a good functional outcome (NDS of ≥60). A cutpoint of >0.523 yielded 81.8% sensitivity and 100% specificity for good outcomes, with an area under the ROC curve of 0.886.

translate these findings to the clinical arena, the effect of EEG artifacts brought about by the clinical environment and patient movement must also be taken into consideration. We anticipate that movement artifact will be minimized with induced hypothermia because pharmacologic paralysis is typically employed to eliminate shivering. Translation of this technology to the clinical environment, however, must occur in parallel with development of innovative signal processing algorithms for artifact rejection without compromising important EEG information.

CONCLUSIONS

Early IQ was sensitive to the benefit of hypothermia and to the harmful effect of hyperthermia postresuscitation and predicted neurologic recovery at 72 hrs. This qEEG method was able to monitor brain recovery and predict functional outcome and mortality. The predictive value was particularly robust during the first 2 hrs after CA. With clinical translation, these experiments have the potential to produce a major shift in how brain recovery is monitored.

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