HHS Public Access

Author manuscript

Conf Proc IEEE Eng Med Biol Soc. Author manuscript; available in PMC 2017 May 09.

Published in final edited form as:

Conf Proc IEEE Eng Med Biol Soc. 2016 August ; 2016: 1846–1849. doi:10.1109/EMBC.2016.7591079.

Multimodel Quantitative Analysis of Somatosensory Evoked Potentials After Cardiac Arrest with Graded Hypothermia

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Abstract

Cardiac arrest (CA) is one of the most prominent causes of morbidity and mortality in adults. Therapeutic hypothermia (TH) is a recommended treatment to improve survival and functional outcome following CA, however, it is unclear what degree of TH is most beneficial. It has been suggested that TH of 33°C provides no survival or outcome benefits over TH of 36°C. Additionally, there is a lack of verified objective quantitative prognostic tools for comatose CA patients under TH. In this study, we calculated three quantitative markers of somatosensory evoked potentials (SSEP) to examine their potential to track recovery in the early period following CA under graded TH. A total of 16 rats were randomly divided among 4 temperature groups (n=4/group): normothermia (N0, 36.5–37.5°C), hypothermia 1 (H1, 30–32°C), hypothermia 2 (H2, 32–34°C) and hypothermia 3 (H3, 34–36°C). All rats underwent a 15min baseline SSEP recording followed by 9min asphyxial-CA, resulting in severe cerebral injury, and immediate temperature management following resuscitation for 6 hours. SSEP recordings were maintained in 15 min intervals from 30min–4hrs after resuscitation. The N10 amplitude, N10 latency and quantitative SSEP phase space area (qSSEP-PSA) were calculated for the early recovery period and normalized to their respective baselines. Functional recovery was determined by the neurological deficit scale (NDS). N10 amplitude was significantly larger in H1, H2 and H3 compared to N0. N10 latency was significantly longer in H1 than all temperature groups and all hypothermia groups had significantly longer latencies than N0. qSSEP-PSA had significantly better recovery in H1 and H2 than N0. Animals with good outcome (72hr NDS≥50) had better recovery of all markers. N10 amplitude was significantly correlated with N10 latency and qSSEP-PSA. The results importantly demonstrate that quantified SSEPs have the potential to objectively track recovery following CA with graded TH.

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I. Introduction

Out-of-hospital cardiac arrest (CA) occurs in almost 360,000 adult Americans annually, with only 10.8% of patients surviving to discharge, of which only 8.5% recover with good functional outcome [1]. Mild therapeutic hypothermia (TH) of 32–34°C is an increasingly common neuroprotective method that has been shown to improve survival and neurological outcome following CA [2]. However, it has not been clearly demonstrated which level of hypothermia is most beneficial to outcome. Multiple grades of hypothermia have been studied [2, 3], but it is unclear which provides the best neuroprotection following CA.

Reliable prognostication during the early recovery period following CA would optimize treatment protocols, resource allocation and information rely to patients' families. While multiple prognostic tools exist, their reliability under hypothermia has been questioned [4]. However, it has been suggested that somatosensory evoked potentials (SSEP) maintain prognostic value under TH [5].

SSEP have proven to be a useful prognostic tool for comatose patients in post-CA recovery. Specifically, the bilateral absence of the N20 peak (negative inflection approximately 20ms after stimulation) is the best predictor of poor outcome [6, 7]. However, even among highly trained experts, the signal interpretation is subjective [8, 9]. Thus, there is a major need for a reliable and objective prognostic tool to track recovery. In this preliminary study, we describe multiple quantitative analyses of SSEP – N10 amplitude and latency and quantitative SSEP phase space area (qSSEP-PSA) – with the potential to track early cerebral recovery following severe brain injury in a 9 min CA rat model with graded hypothermia. We tested the potential prognostic value of these markers under graded hypothermia and discovered that SSEPs hold potential predictive value in the form of graded quantitative markers that extend beyond the dichotomous categorization of peaks.

II. Methods

A. Animals

In this preliminary study, a total of 16 adult male Wistar rats (371±12 g) underwent 9 min asphyxial-CA, which rats were expected to survive but with severe brain injury. The animals were randomly assigned to normothermia or one of three grades of hypothermia (n=4/group): N0 (36.5–37.5°C), H1 (30–32°C), H2 (32–34°C), H3 (34–36°C). All procedures were approved by the University of Maryland Animal Care and Use Committee.

B. Electrode Implantation

Approximately 3 days before the date of CA, rats underwent an implantation procedure. Each rat had 4 screw electrodes (Plastics One, Roanoke, VA) cortically implanted over the forelimb and hindlimb regions of the somatosensory cortex. One electrode was placed over the parasaggital right frontal lobe as a ground. The screws were held in place with a plastic pedestal and dental cement [10, 11].

C. Cardiac Arrest and Temperature Control

The asphyxial-CA and resuscitation procedures were performed as previously described [10, 12–14]. Rats were intubated and continuously anesthetized with 1.5% isofluorane in 1:1 O2:N2, delivered by a mechanical ventilator. Drug administration, mean arterial pressure (MAP) monitoring and arterial blood gases (ABG) measurement were done via the cannulated femoral vein and artery. The rats had 15 min baseline SSEPs recorded followed by a 5 min anesthetic washout period, consisting of 2 min of 100% oxygen followed by 3 min of room air, during which Vecuronium (2 mg/kg) was administered to induce muscle paralysis. Following the washout, the breathing tubes were clamped and the ventilator was disconnected to initiate asphyxia. After 9 min of CA (MAP < 10 mmHg), cardiopulmonary resuscitation (CPR) was performed using sternal chest compressions, 100% oxygen, epinephrine and sodium bicarbonate until the return of spontaneous circulation (ROSC, MAP > 60 mmHg). SSEP recordings were taken in 15 min intervals from 30 min-4 hrs after ROSC. Isofluorane was administered as needed (up to 0.5%) once SSEP recordings began during the recovery period due to the potential discomfort of the stimulations.

Temperature management began immediately after ROSC was achieved. Temperature was measured by a rectal probe and was closely monitored and recorded every 5min. The hypothermic animals were immediately surface cooled using a water and alcohol mist and a small electric fan. The hypothermia rats were maintained at their appropriate degree of hypothermia (H1 30–32°C, H2 32–34°C, H3 34–36°C) for 6 hours after ROSC. After 6 hours, the animals underwent slow rewarming to normothermia (36.5–37.5°C) at a rate of 1°C per 30 min. The normothermia animals were maintained at 36.5–37.5°C for 6 hours after ROSC using a heating pad.

D. SSEP Acquisition and Analysis

The SSEP signals were recorded from the skull electrodes following stimulation of the median nerves. Stimulation pulses (200usec, 6mA) were delivered to subdermal electrodes at a frequency of 0.5Hz. The subsequent SSEPs were recorded with the TDT System3 data acquisition system (Tucker-Davis Technologies, Alachua, FL) at a frequency of 6.1kHz.

The SSEPs were recorded for 15 min prior to CA (baseline) and beginning 30 min after ROSC, continuing in 15 min intervals until 4 hrs after ROSC. The sweeps within each 15 min interval were averaged (450 sweeps) and the quantitative analyses were performed on the averaged waveform for each time period and then normalized to baseline values. The normalized values for all time periods were used to generate the aggregate value for each quantitative marker. Animals with abnormal baseline waveforms (bilaterally distorted N10 and P15) were excluded from the analysis.

N10 amplitude and latency—The rat N10 peak (negative inflection approximately 10ms after stimulation) is equivalent to the N20 peak in humans. The N10 amplitude was measured as the peak-to-peak amplitude between the N10 and P15 (positive inflection 15ms after stimulation) peaks. The N10 latency was measured as the time from stimulation to the N10 peak. The amplitude and latency were measured manually using a custom MATLAB (MathWorks, Natick MA) algorithm.

qSSEP-PSA—The qSSEP-PSA marker was calculated as previously described [10]. Briefly, the phase space curve (PSC) of an SSEP waveform was generated by plotting the first derivative against the magnitude, thus capturing the morphologic information of the peak. The phase space area (PSA), a representation of the signal power, was calculated by determining the area bound by the PSC. This qSSEP-PSA was determined by using the Quickhull algorithm [15] to fit a convex hull to the PSC. The point-index based convex hull was calculated by identifying the indices of the PSC that exist along the boundary of the convex hull and the qSSEP-PSA is the area encompassed by this boundary. The algorithm selects points within the waveform, including transitional slopes and smaller peaks, as to capture the extent of the signal, therefore encompassing more information than merely an amplitude or latency. These analyses were performed using MATLAB [10].

E. Neurologic Recovery Assessment

The neurologic recovery of rats was assessed using the neurologic deficit scale (NDS) at 6, 24, 48 and 72 hrs after ROSC. Rats were given a score ranging from 0 (worst) to 80 (best) based on performance of various motor and stimuli reaction tests [10–13]. The 72 hr NDS was used to determine the final functional outcome such that good functional outcome was defined as 72 hr NDS ≥ 50 and poor functional outcome as 72 hr NDS < 50 [10].

F. Statistics

A commercial computer package (IBM SPSS Statistics v22, Armonk, NY) was used for all statistical analyses. The N10 amplitude and latency, and qSSEP-PSA (mean±S.E.M.) were compared between temperature groups using a repeated measure of analysis of variance (ANOVA) and compared between outcome groups using a student's t-test. Bivariate analyses were used to generate the pearson correlation coefficients between quantitative markers. A p value < 0.05 was considered statistically significant.

III. Results

A. Temperature, NDS, and Baseline Data

The temperature was well monitored throughout the duration of the experiment. The groups were maintained at their respective temperature ranges: H1 (31.2±0.06°C), H2 (33.0±0.05°C), H3 (34.7±0.04°C), N0 (37.1±0.03°C). Target temperatures were reached within 11±2min (H1: 18±3min; H2: 10±2min; H3: 5±0min). Based on the 72 hr NDS (median (25^{th}, 75^{th} percentiles)), 7 animals had poor outcome (0 (0,0)) and 9 animals had good outcome (66 (57,71)) ($p<0.01$). The baseline rat body weight was not significantly different among temperature groups ($p>0.05$).

B. N10 Amplitude

The N10 amplitude of the early recovery period (first 4 hours after ROSC) showed a decreasing trend among increasing temperature groups (Fig. 1A). All three hypothermia groups (H1, H2 and H3) had significantly larger N10 amplitudes than the normothermia (N0) group (all $p<0.05$). The H1 group also had significantly larger N10 amplitudes than the H3 group ($p<0.01$). Animals with good outcome also had better N10 amplitude recovery

compared to those with poor outcome, though the difference was not significant with the current animal cohort ($p>0.05$) (Fig. 1B).

C. N10 Latency

The early recovery N10 latency showed a decreasing trend among increasing temperature groups (Fig. 2A). All hypothermia groups (H1, H2, and H3) had significantly longer N10 latencies than the normothermia group (N0) (all $p<0.01$). The H1 and H2 groups also had significantly longer latencies than the H3 group ($p<0.01$) and the H1 group had significantly longer latencies than the H2 group ($p<0.01$). Animals with good outcome also had significantly longer N10 latencies than those with poor outcome ($p<0.05$) (Fig 2B).

D. qSSEP-PSA

The qSSEP-PSA during the early recovery was significantly larger in the H1 and H2 groups than the N0 group ($p<0.01$) (Fig. 3A). The H3 qSSEP-PSA was lower than the H1 and H2 groups and larger than N0, though the differences were not significant ($p>0.05$). qSSEP-PSA was also higher in animals with good outcome compared to those with poor outcome, although the difference was not significant ($p>0.05$) (Fig. 3B).

E. Correlation Between Quantitative Markers

Among the quantitative markers, the N10 amplitude was significantly correlated with both N10 latency (pearson correlation coefficient: 0.400, $p<0.01$) (Fig. 4A) and qSSEP-PSA (pearson correlation coefficient: 0.904, $p<0.01$) (Fig. 4B).

IV. Discussion

In this study, the integrity of the somatosensory pathway following severe brain injury by asphyxial-CA was examined using multiple quantitative markers under graded hypothermic conditions, for the first time. We discovered that quantitative SSEPs hold great potential to track recovery following CA with TH by providing continuous quantitative criteria, thereby accounting for multiple conditions as opposed to dichotomous categorization of peak presence. All three markers, N10 amplitude and latency, and qSSEP-PSA, demonstrated clear trends among both temperature and functional outcome groups. This experiment demonstrates the potential prognostic value of these novel quantitative markers for the early recovery after severe CA with graded TH.

The majority of studies evaluating the prognostic value of SSEP following CA are focused on the bilateral absence of N20 [4, 6, 7] rather than the relationship between quantitative SSEP measures and outcomes. Only one human study has examined the relationship between SSEP amplitude and outcome, suggesting a threshold amplitude voltage to distinguish good and bad outcomes [16]. However, the study does not use specific response peaks in the evaluation of amplitude. Here we provide three quantitative, objective and repeatable SSEP markers that hold potential prognostic value following CA with temperature management.

Our previous work developed the qSSEP-PSA marker and demonstrated the potential prognostic value of both qSSEP-PSA and N10 amplitude in normothermic animals with moderate and severe brain injuries following CA [10]. This study showed that animals with moderate injury had better qSSEP-PSA recovery than those with severe injury. Here we demonstrated that qSSEP-PSA had better recovery with deeper hypothermia (H1 and H2) compared to normothermia and in animals with good outcome compared to poor outcome. The qSSEP-PSA marker also mirrored the median 72 hr NDS among temperature groups (H2 > H1 > H3 > N0, data not shown). The PSA marker is a strong measure of SSEP waveforms as it considerers multiple features of the entire signal rather than a single response peak characteristic.

The N10 amplitude and latency have been previously studied in both moderate and severe brain injury under normothermic conditions [11]. This study demonstrated that amplitude recovery is better after moderate injury than severe injury and that latency decreases towards baseline over the early recovery period at both injury severity levels. The present study demonstrated better recovery of N10 amplitude in animals treated with lower temperature grades and with good functional outcome and that N10 latency was overall longer than baseline in animals with deeper hypothermia and good outcome. Although our previous study has shown that hypothermia increases N10 amplitude and latency compared to normothermic groups in an uninjured rat model [17], it has been suggested that the effect of mild hypothermia (33°C) does not have a significant effect on the relationship between SSEP amplitude and outcome in a human study [16].

SSEP amplitude has been shown to be related to functional outcome [16]. Here we demonstrate that N10 amplitude is correlated with both N10 latency and qSSEP-PSA during the early recovery from severe brain injury with graded hypothermia. Thus, the prognostic potential of these quantitative SSEP markers, N10 amplitude, N10 latency, and qSSEP-PSA, is further demonstrated.

Although clear trends of the quantitative SSEP markers were demonstrated in this study, the results must be interpreted with caution, as this is a preliminary study with small animal numbers. The use of 72 hr NDS among temperature groups to evaluate the effect of graded hypothermia was not our focus in the present study due to the low power of the small animal number, though the trend generally followed that of the quantitative markers (median NDS higher in the H1 and H2 groups and lowest in N0, data not presented).

Thus, the data we present here corroborates previous studies of N10 amplitude and qSSEP-PSA under normothermic conditions and it is necessary to extend the present study with larger animal numbers, including a sham group. The quantitative SSEP markers presented here demonstrated prognostic potential following severe CA with graded hypothermia.

Acknowledgments

Research supported by R01HL118084 from NIH (to XJ).

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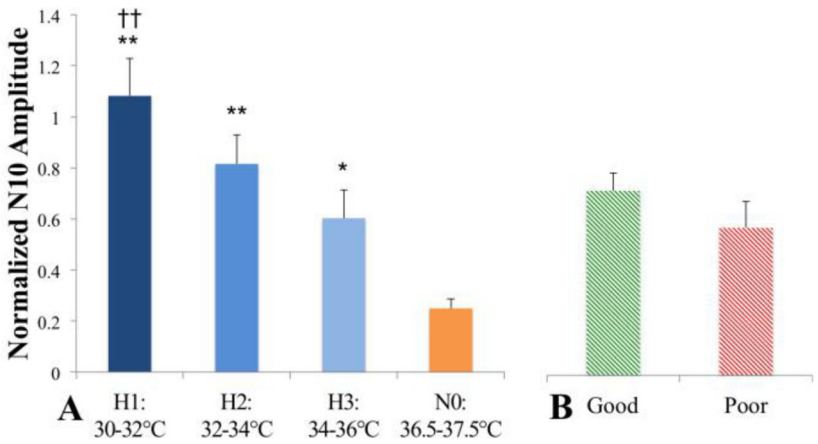

Figure 1.

A) Normalized aggregate N10 amplitude among four temperature groups. All three hypothermia groups (H1, H2, H3) had significantly larger N10 amplitudes than N0. H1 also had significantly larger amplitude than H3. B) Normalized aggregate N10 amplitude was higher in animals with good functional outcome with no significance. * $p < 0.05$, ** $p < 0.01$ compared to N0. †† $p < 0.01$ compared to H3.

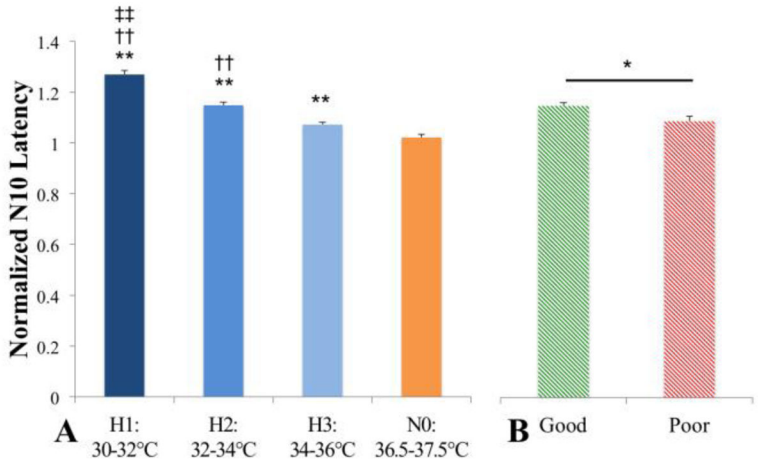

Figure 2.

A) Normalized aggregate N10 latency among four temperature groups. All three hypothermia groups (H1, H2, H3) had significantly longer N10 latencies than N0. H1 also had significantly longer latency than H2 and H3 while H2 had significantly longer latency than H3. B) Normalized N10 latency was significantly longer in animals with good outcome. ** $p < 0.01$ compared to N0. †† $p < 0.01$ compared to H3. ‡‡ $p < 0.01$ compared to H2.

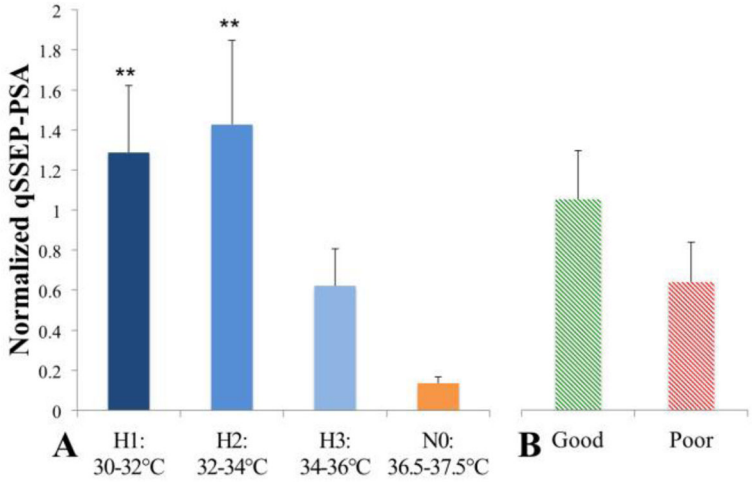

Figure 3.

A) Normalized aggregate qSSEP-PSA among four temperature groups. Both H1 and H2 had significantly larger qSSEP-PSA values than N0. B) qSSEP-PSA was higher in animals with good outcome but the difference was not significant with the current animal cohort. ** $p < 0.01$ compared to N0.

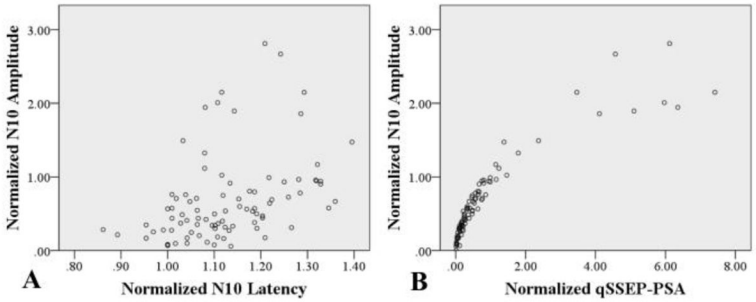

Figure 4.
N10 amplitude was significantly correlated to A) N10 latency and B) qSSEP-PSA.