The Prognostic Value of Somatosensory Evoked Potentials in Children After Cardiac Arrest: The SEPIA Study

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Purpose: Absent cortical somatosensory evoked potentials (SSEPs) reliably predict poor neurologic outcome in adults after cardiac arrest (CA). However, there is less evidence to support this in children. In addition, targeted temperature management, test timing, and a lack of blinding may affect test accuracy.

Methods: A single-center, prospective cohort study of pediatric (aged 24 hours to 15 years) patients in which prognostic value of SSEPs were assessed 24, 48, and 72 hours after CA. Targeted temperature management (33–34°C for 24 hours) followed by gradual rewarming to 37°C was used. Somatosensory evoked potentials were graded as present, absent, or indeterminate, and results were blinded to clinicians. Neurologic outcome was graded as “good” (score 1–3) or “poor” (4–6) using the Pediatric Cerebral Performance Category scale 30 days after CA and blinded to SSEP interpreter.

Results: Twelve patients (median age, 12 months; interquartile range, 2–150; 92% male) had SSEPs interpreted as absent (6/12) or present (6/12) <72 hours after CA. Outcome was good in 7 of 12 patients (58%) and poor in 5 of 12 patients (42%). Absent SSEPs predicted poor outcome with 88% specificity (95% confidence interval, 53% to 98%). One patient with an absent SSEP had good outcome (Pediatric Cerebral Performance Category 3), and all patients with present SSEPs had good outcome (specificity 100%; 95% confidence interval, 51% to 100%). Absence or presence of SSEP was consistent across 24-hour (temperature = 34°C), 48-hour (t = 36°C), and 72-hour (t = 36°C) recordings after CA.

Conclusions: Results support SSEP utility when predicting favorable outcome; however, predictions resulting in withdrawal of life support should be made with caution and never in isolation because in this very small sample there was a false prediction of unfavorable outcome. Further prospective, blinded studies are needed and encouraged.

Key Words: Somatosensory evoked potential, Targeted temperature management, Prognosis, Pediatrics, Cardiac arrest, Hypoxic ischemic injury.

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Accurate prediction of neurologic outcome in children who remain comatose after cardiac arrest (CA) is important as uncertainty may impair decision making, delay appropriate management, and compound the stress and anxiety of families.1 Somatosensory evoked potentials are well described and recommended to predict poor outcome in adults after CA.2–5 In 2014, previous prospective parameters were updated to reflect changes in CA management (therapeutic hypothermia), advances in diagnostic imaging, such as EEG and MRI, and address limitations in prognostic studies (self-fulfilling prophecy bias in unblinded studies).6 Bilateral absence of N20 potentials still have high specificity (>90%) and a false-positive rate of between 0% and 3% with slightly higher FPRs in those treated with therapeutic hypothermia.7,8 However, a recent systematic review suggested that false-positive rates may be up to 10 times higher than previously thought.9 Pediatric cohorts were excluded from this review, so we are still unsure as to what the false-positive rate is in pediatric prognostic SSEPs.

Currently, SSEPs performed >72 hours after CA are used as part of multimodal prognostic algorithms, but there is still a lack of blinded research in this field.6–10 and it is difficult to apply current guidelines and recommendations to pediatric practice because the majority of evidence cited largely excludes those younger than 16 years.5,11,12 Although test accuracy is similar in pediatric patients,13 caution is advised when predicting poor outcome because awakening can occur despite bilaterally absent N20 cortical potentials.14 Somatosensory evoked potentials are generated via the summation of peripherally evoked potentials which synapse at the dorsal root entry zone of the spinal cord and ascend ipsilaterally to the cuneate nucleus, decussating below the level of the thalamus and traveling to the contralateral post-central gyrus/somatosensory cortex.15 Electrophysiologically, this is represented as a negative deflection occurring 20 ms (N20) after upper limb stimulation and 35 ms (N35) in lower limbs. If bilaterally absent, in the presence of peripheral and spinal potentials, severe neurologic injury is indicated.15 Although there is concern that low false-positive rates and high-test specificity may be exaggerated because of unblinded studies,
guidelines recommend their use when predicting poor outcome in comatose CA survivors. Despite this, prognostic SSEPs are not considered an essential investigation in all United Kingdom intensive care units (ICUs), and MRI or EEG is more commonly used. Perhaps because SSEP testing requires expertise in implementation and interpretation, which is not available nationally, and the moderate interobserver variation among experts when interpreting the N20 as absent. In addition, albeit rarely, absent N20 responses incorrectly predict poor outcome if performed during targeted temperature management (TTM) (24–48 hours of body core temperature reduction to 33–34°C) or <72 hours after CA, a finding more frequently reported in the pediatric age range. Current guidelines suggest prognostication in comatose CA patients with absent or extensor motor response to pain should not be performed <72 hours after return of spontaneous circulation; however, early prognosis is preferred as decisions regarding withdrawal of life sustaining therapy may already be firmly established at 72 hours after CA and thus for SSEPs to be beneficial in the pediatric intensive care setting they must be reliable early and during TTM. Several studies report on the reliability of SSEP performed during TTM (33–34°C), but current opinion suggests that SSEPs should only be performed >72 hours after return of spontaneous circulation if treated with TTM (33–34°C).

The objective of this study was to assess whether blinded SSEPs could accurately predict neurologic outcome 30 days after CA in children and whether TTM (33–34°C) or the timing of the SSEP test affected its prognostic accuracy.

METHODS

This single-center prospective cohort study was performed in a tertiary pediatric ICU (PICU) in the United Kingdom. Patients included were aged between 0 and 15 years, admitted to PICU after CA with cardiopulmonary resuscitation duration greater than 3 minutes and remained comatose. Patients were excluded because of lack of parent/guardian consent or unwillingness of the patient’s consultant to allow inclusion in the study, if they were ineligible for SSEP monitoring (e.g., spinal cord injury), or if the patient had a preexisting condition affecting the integrity of the SSEP (e.g., a peripheral neuropathy). Informed consent was obtained from the child’s parent/guardian within 24 hours of CA. The study was approved by the Coventry & Warwickshire Regional Ethics Committee, United Kingdom [REC REF no. 13/WM/0123].

Standard after CA management during part of the study recruitment period (2013–2014) included TTM, using a core temperature of 33 to 34°C for 24 hours with active rewarming over 16 hours to 37 to 37.5°C. Patients were sedated with morphine and midazolam infusions and received rocuronium to achieve neuromuscular blockade if required to avoid shivering or ventilator synchrony during TTM.

Serial SSEPs were recorded in line with published guidelines, with the exception of recording a far-field subcortical potential, at 24, 48, and 72 hours after CA by stimulating the median nerve aspect of the wrist or elbow and recording cortical evoked potentials (EPs) from C3 and C4 (located 2 cm posterior to C3/C4 International 10:20 placement); spinal EPs from cervical vertebra 2 or 5 and peripheral EPs from Erb’s point (located at the upper trunk of the brachial plexus, 2–3 cm above the clavicle) or the median aspect of the elbow if access to Erb’s point was not possible. The stimulus was administered via bipolar surface electrodes at a rate of 2.1 Hz. Stimulation duration was 0.2 to 0.5 ms, set at an intensity 1.5 times higher than motor threshold, or at 25 mA if neuromuscular junction blocking agents were administered. Two sets of 150 summated EPs were recorded within 3 Hz and 3 kHz low- and high-frequency filters using either Medelec Synergy (Viasys, Woking, United Kingdom) or Myoquick matrix line (Micromed, Working, United Kingdom) recording software.

Somatosensory evoked potentials were analyzed by one consultant clinical neurophysiologist (L.N.) and documented as “absent” (defined as a bilaterally absent N20 response after left and right median nerve stimulation in the presence of peripheral or cervical responses), “present” (Cortical N20 response after left and right median nerve stimulation), or “indeterminable” (technically insufficient recording). In the case of a unilateral indeterminable SSEP, the contralateral response was used. The reporting clinical neurophysiologist was masked to all patient details except limb length and core temperature. Pediatric ICU staff were masked to SSEP results.

Neurodevelopmental and survival outcome was assessed by one assessor (T.R.) using the Pediatric Cerebral Performance Category (PCPC) scale30 30 days after CA either via face-to-face or telephone interviews with parent/guardian. Pediatric Cerebral Performance Category is a 6-point scale (1 = normal, 2 = mild disability, 3 = moderate disability, 4 = severe disability, 5 = coma or vegetative state, and 6 = death), and primary outcome was poor neurodevelopmental outcome (PCPC 4–6).

Secondary questions were whether the presence of SSEPs predicted good neurodevelopmental outcome (PCPC 1–3) and the effect SSEP timing and TTM (33–34°C) had on the SSEP. Twenty-four-hour SSEPs were performed during TTM (33–34°C), 48-hour SSEPs during the rewarming phase, and 72-hour SSEPs when normothermic.

Peak onset latency of cortical EPs, nerve conduction velocities, and SSEP interpretability (i.e., too much artefact to prevent analysis) were recorded for each trace. Demographic and Utstein defined resuscitation variables30 (age, sex, location of arrest, first monitored cardiac arrhythmia, and time to return of spontaneous circulation) were collected for each patient.

Statistical Analysis

Basic summary statistics are reported for the entire study population. Binary and categorical variables are summarized using numbers and percentages. Continuous variables are summarized using mean and SD (for normally distributed variables) or median and interquartile range (for variables that are not normally distributed). The choice of summary statistics for continuous variables was made after viewing a histogram. For each outcome, a 2 × 2 table of outcome against prediction was created. From this table, sensitivity (true-positive rate), specificity (true-negative rate), positive predicted value, negative
predicted value, and rates of type I and II error were calculated. The combination of these measures allowed us to provide some description of the possible prognostic accuracy of SSEP. Paired t-tests were used to examine whether there was a difference in onset latency and conduction velocity recorded from the same patient at any of the three different time points SSEPs were acquired (24, 48, 72 hours). A P value < 0.05 was considered significant. A binomial approximation was made when calculating 95% confidence intervals (CIs) for the predictive measures. All analysis was performed using Minitab 17.

RESULTS

Between August 2013 and December 2014, 18 patients were admitted to PICU after CA, 16 met inclusion criteria (as 2 had cardiopulmonary resuscitation <3 minutes after CA) and 12 (75%) were successfully recruited. Lack of consent from families (n = 3) and from lead consultant (n = 1) were the reasons for exclusion. Baseline demographics, resuscitation factors, and outcomes are presented in Table 1. A significant proportion (92%) were male and the majority received TTM (33–34°C), of which 4 (33%) died and 1 was severely disabled 30 days after CA. Cause of death was hypoxic ischemic injury after CA in all patients. Ventricular fibrillation (33%) and asystole (33%) were the most common presenting rhythms. Eight (67%) patients survived, 3 (33%) with good outcome (PCPC 1), 3 (33%) with minor disabilities (PCPC 2), 1 (8%) with moderate disability (PCPC 3), and one (8%) with severe disability (PCPC 4).

### TABLE 1. Demographics and Resuscitation Factors of the 12 Patients Recruited

| Demographic and Resuscitation Factors | Total, n = 12 |
|---------------------------------------|--------------|
| Age, months, median (IQR)              | 12 (2–150)   |
| Gender, male (%)                      | 11 (92)      |
| Presenting rhythm, n (%)              |              |
| VF                                    | 4 (33)       |
| Asystole                              | 4 (33)       |
| PEA                                   | 1 (8)        |
| Bradycardia                           | 1 (8)        |
| Unknown                               | 2 (17)       |
| Location of cardiac arrest, n (%)     |              |
| In-hospital                           | 3 (25)       |
| Out-of-hospital                       | 9 (75)       |
| TTM (33–34°C) use, n (%)              | 10 (83)      |
| ROSC, minutes, median (IQR)           | 25 (14–39)   |
| PCPC score, n (%)                     |              |
| 1                                     | 3 (25)       |
| 2                                     | 3 (25)       |
| 3                                     | 1 (8)        |
| 4                                     | 1 (8)        |
| 5                                     | 0            |
| 6                                     | 4 (33)       |

CA, cardiac arrest; CPR, cardiopulmonary resuscitation; IQR, interquartile range; PEA, pulseless electrical activity; PCPC, Pediatric Cerebral Performance Category; ROSC, return of spontaneous circulation; TTM, targeted temperature management; VF, ventricular fibrillation.

Median time from CA onset to first, second, and third SSEP recordings were 25 hours (interquartile range, 24.3–28.0), 48 hours (interquartile range, 46.6–50.8), and 73 hours (interquartile range, 70.0–74.5), respectively. Mean body temperature was 34.0°C (SD 0.8) during TTM (33–34°C) period, 36.3°C (SD 1.4) during rewarming, and 36.7°C (SD 0.4) when normothermic.

Sixty-eight SSEPs (34 from left limb stimulation and 34 from right limb) were recorded in 12 patients: 20 during TTM (33–34°C), 20 during rewarming, and 28 while normothermic (36.5–37.5°C). Progressively more SSEPs were available for analysis over serial recordings (Table 2) for 2 reasons: a change in PICU practice meant TTM (33–34°C) was not administered in 2 patients and artefact contamination seemed more problematic in 24- and 48-hour recordings, thus 13 SSEPs (recorded in three patients) were deemed indeterminate during TTM (33–34°C) (n = 6), rewarming (n = 5), and normothermia (n = 2). Absent/present interpretations were reached in all patients before 72 hours. In total, 16 (in 8 patients), 19 (in 10 patients), and 20 (in 11 patients) SSEPs were analyzed in 24-, 48-, and 72-hour groups, respectively (Table 2).

An absent cortical SSEP incorrectly predicted poor outcome in one patient (Fig. 1) (88% specificity; 95% CI, 53% to 98%); therefore, the rate of false predictions was 13% (95% CI, 0% to 45%) and PPV was 80% (95% CI, 45% to 100%). Present cortical SSEPs correctly predicted good outcome with 100% specificity (95% CI, 51% to 100%) but lower sensitivity (86%; 95% CI, 49% to 97%) (Table 3). Specificity and PPV were lower in 72-hour recordings because 24- and 48-hour SSEPs of the false positives were interpreted as indeterminate because of excess artefact and excluded from analysis. The presence or absence of cortical potentials at 24 hours was consistent within serial recordings. When warmed from TTM (33–34°C), peak onset latency of peripheral, spinal, and cortical EPs decreased and nerve conduction velocity (both peripheral and central) increased (Table 4).

DISCUSSION

In this small prospective cohort study, blinded SSEPs predicted outcome accurately in most patients and the timing of the SSEP test or temperature of the patient did not significantly impact on prognostic accuracy. However, one patient with absent cortical potentials at 72 hours after CA had good (PCPC 3) neurologic recovery. If this patient’s SSEPs were not blinded to PICU clinicians, and considered in prognostic algorithms, it may have resulted in a decision to withdraw life-sustaining therapy. Although we advise caution when using SSEPs in isolation to predict poor outcome in pediatric comatose CA survivors, these findings are overstated by our small sample size, and conclusions must be considered with this in mind.

Bilaterally absent cortical SSEPs have been reported in pediatric, traumatic brain injury, CA, and meningitis “good-outcome” patients.5,13,14 These studies highlight the importance of delaying prognosis to ensure electrical interference, interobserver variation, sedation, and antiepileptics do not limit SSEP-based prognosis. However, even when accounted for and minimized, false positives still occur infrequently.20–23,31
Absent SSEPs in pediatric CA after traumatic brain injury have lower specificity in predicting poor outcome when compared with brain injury as a result of hypoxic ischemic encephalopathy, and the presence of cortical SSEPs has a higher diagnostic odds ratio to predict awakening when compared with hypoxic ischemic encephalopathy.\(^\text{14,32}\) Even though a traumatic brain injury patient in the present study had poor outcome correctly predicted at 24, 48, and 72 hours after CA, we believe SSEPs performed within 24 hours of traumatic brain injury should be repeated.

Our false positives had no known comorbidities that could explain an absent SSEP. Sedation was not excessive and not significantly altered during TTM (33–34°C). Technically, the SSEP was difficult to record and deemed indeterminate at 24- and 48-hour recordings because of interference but was interpreted as absent at 72 hours (Fig. 1).

### TABLE 2. Interpretation of Serial SSEPs Performed After Left and Right Limb Stimulation and 30-Day Outcome Assessed Via PCPC Score

| Participant | Interpretation of SSEP | 24 Hours | 48 Hours | 72 Hours | Total SSEPs included into statistical analysis |
|-------------|------------------------|----------|----------|----------|---------------------------------------------|
| Left | Right | Left | Right | Left | Right | Left | Right |
| S01 | Ind. | Ind. | Ind. | Ind. | Absent* | Absent* | Moderate disability/3 |
| S02 | Present | Present | Present | Present | Present* | Present* | Mild disability/2 |
| S03 | Ind. | Ind. | Ind. | Ind. | Ind.* | Present* | Normal/1 |
| S04 | Absent | Absent | Absent | Absent | Absent* | Absent* | Death/6 |
| S05 | Present | Present | Present | Present | Present* | Present* | Normal/1 |
| S06 | Present | Present | Present | Present | Present* | Present* | Normal/1 |
| S07 | Absent | Absent | Absent | Absent | Absent* | Absent* | Severe disability/4 |
| S08 | Present | Present | Present | Present | Present* | Present* | Mild disability/2 |
| S09 | Ind. | Ind. | Ind. | Ind. | Ind.* | Absent* | Death/6 |
| S10 | Absent | Absent | Absent | Absent | Absent* | Absent* | Death/6 |
| S11 | N/A | N/A | Absent* | Absent* | N/A | N/A | Death/6 |
| S12 | Present* | Present* | Present* | Present* | Present* | Present* | Mild disability/2 |

Total SSEPs included into statistical analysis
- Left/right 8 8 9 10 9 11 26 29
- Total 16 19 20 55

*Total SSEPs included from left and right limbs over serial recordings detailed separately.*

Ind, indeterminate SSEP; N/A, not performed and patient did not receive; PCPC, Pediatric Cerebral Performance Category; SSEP, somatosensory evoked potential; TTM, targeted temperature management.

FIG. 1. Top: 72-hour right and left limb SSEPs interpreted as bilaterally absent in a patient with good outcome (PCPC 3) 30 days after CA. Bottom: 72-hour right and left limb SSEPs interpreted as bilaterally present in a patient with good outcome (PCPC 1). Peripheral, spinal, and cortical waveforms displayed in top, middle, and bottom lines, respectively. Peripheral responses recorded from Erb’s point (top trace) and median aspect of elbow (bottom trace). CA, cardiac arrest; PCPC, Pediatric Cerebral Performance Category; SSEP, somatosensory evoked potential.
TABLE 3. Predictive Power of Absent and Present Cortical SSEPs at 24, 48, and 72 Hours After Cardiac Arrest

| Predictive Power Calculations | Absent Cortical SSEPs | Present Cortical SSEPs |
|-------------------------------|-----------------------|------------------------|
| Time                          | 24 Hours              | 48 Hours               | 72 Hours               | 72 Hours               |
| Temperature, °C, mean (±SD)   | 34.0 (0.8)            | 36.3 (1.4)             | 36.7 (0.4)             | 37.1 (0.5)             |
| Sensitivity, % (95% CI)       | 100 (48–100)          | 100 (56–100)           | 100 (56–100)           | 86 (49–97)             |
| Specificity, % (95% CI)       | 100 (51–100)          | 100 (61–100)           | 88 (53–98)             | 100 (51–100)           |
| PPV, % (95% CI)               | 100                   | 100                    | 80 (45–100)            | 100                    |
| NPV, % (95% CI)               | 100                   | 100                    | 100                    | 80 (45–100)            |
| FPR, % (95% CI)               | 0                     | 0                      | 13 (0–45)              | 0                      |

CI, confidence interval; FPR, false-positive rate; NPV, negative predictive value; PPV, positive predictive value; SSEP, somatosensory evoked potential.

Interpreting serial SSEPs between hypothermic (TTM [33–34°C]) and normothermic conditions did not alter the prognostic accuracy of the test. Since 2002, a growing body of literature emerged supporting survival in CA patients treated with TTM (33–34°C), which raised concerns regarding the accuracy of prognostic tests performed during hypothermia. Several studies addressed this issue, and guidelines support SSEP prognostication at 24 hours if no TTM (33–34°C) is used, and at 72 hours if used. Rationale for delayed prognosis was the increased rate of false predictions seen in TTM-treated (33–34°C) patients. These were attributed to excessive artefact and an increased rate of interobserver variation. In the current study, an accurate prognosis was determined at 24 hours in the majority (66%) of patients. However, exclusion of SSEP traces because of excessive artefact was highest in the 24-hour group (n = 6) in comparison with the 48-hour (n = 5) and 72-hour (n = 2) group. During rewarming, increasing body temperature was associated with decreasing latency of EPs and increase in peripheral and central nerve conduction velocity in keeping with previous studies. The lack of statistical significance could be because of small sample size.

There are limitations to the study. First, interobserver variation was not formally assessed and has been described as moderate to substantial when interpreting prognostic SSEPs, and should be addressed in future studies. Second, PCPC uses school-based and age-specific criteria to assess good and bad outcome categories. There remains disagreement as to whether PCPC 1 to 2 or 1 to 3 demonstrates a good outcome and whether moderate disability is good/poor outcome after CA. In pediatric age (3–19 years), 97% of patients with absent SSEPs and 92% of patients with present SSEPs have outcome predicted correctly, which is similar to presented findings. Sensitivity is low in adults (48%–100%) because present cortical responses do not ensure good outcome. Sensitivity in pediatrics may be higher because of infant brain plasticity and the marked difference in favorable ICU prognosis in comparison with adults. We found that a present cortical SSEP identified the majority (86%) of good outcome patients, although this may be an optimistic estimate in our small, heterogeneous sample.

A strength of this study was that SSEP results were successfully blinded from clinical staff caring for the patient and clinical data from the neurophysiologist interpreting SSEPs. The rate of false predictions was higher than previously described but we must emphasize that findings are likely because of small sample size. We believe the current findings add to the clinical utility of prognostic SSEPs, and multimodal approaches to CA coma prognostication are essential to minimize the risk of making false predictions.

TABLE 4. Combined Left and Right Peak Onset Latency of Peripheral, Spinal, and Cortical Evoked Potentials After Median Nerve Stimulation at the Wrist; Peripheral and Central Nerve Conduction Velocities

| Core Temperature, Mean (±SD) | Peak Onset Latency, m/s, Mean (SD) | Nerve Conduction Velocity, m/s, Mean (SD) |
|------------------------------|------------------------------------|------------------------------------------|
|                              | Peripheral Spinal Cortical         | Peripheral Central                       |
| Hypothermia, 34 (0.83)       | 6.7 (3.1) 11.7 (2.2) 19.7 (3.3)    | 30.4 (14) 33.2 (4.3)                     |
| Normothermia, 36.7 (0.43)    | 6 (2.4) 10.5 (1.9) 18.7 (4)        | 36.5 (17.6) 38.8 (7.7)                   |
| Difference                   | 0.7 (2.5) 1.2 (1.3) 1 (3.1)        | 6.1 (8) 5.6 (5)                          |

*p < 0.05
Accurate prognosis of comatose CA children is challenging and false-positive SSEP results can occur. Our study supports the utility of SSEPs to predict favorable and unfavorable neurologic outcome irrespective of the time performed or patient temperature. However, caution is advised when using the SSEP in isolation to predict outcome.

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