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The prognostic value of Somatosensory Evoked Potentials In children after cardiac Arrest: The SEPIA study

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Conflicts of interest: None to declare

Preliminary results of this study were presented at the 5th International Hypothermia and Temperature Management Symposium, Edinburgh, 7th-10th September 2014.

RUNNING TITLE: The SEPIA study

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KEY WORDS: SOMATOSENSORY EVOKED POTENTIAL, TARGETED TEMPERATURE MANAGEMENT, PROGNOSIS, PAEDIATRICS, CARDIAC ARREST, HYPOXIC ISCHAEMIC INJURY

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

Methods: A ~~Single~~ single centre, prospective cohort study of paediatric (aged 24-hours – 15years) patients in which prognostic value of SSEPs were assessed 24, 48 & 72 hours post CA. TTM (33-34°C for 24 hours) followed by gradual rewarming to 37°C was used. SSEPs were graded as present, absent, or indeterminate and results blinded to clinicians. Neurological ~~O~~outcome was graded as "Good" (score 1-3) or "Poor" (4-6) using the Paediatric Cerebral Performance Category (PCPC) scale 30 days post CA and blinded to SSEP interpreter.

Results: ~~12~~ Twelve patients (Median age: 12 months; IQR:2-150; 92% Male) had SSEPs interpreted as absent (6/12) or present (6/12) <72 hours post CA. Outcome was good in 7/12 (58%) and poor in 5/12 (42%). Absent SSEPs predicted poor ~~neurological~~ outcome ~~in the majority of patients~~ with 88% specificity (95%CI: 53%-98%) . One patient with an absent SSEP had good (PCPC:3) outcome ~~(Specificity: 88%; 95%CI: 53%-98%)~~ and all patients with present SSEPs had good outcome (Sensitivity: 100%; 95%CI: 40%-100%). SSEP absence/presence was consistent across 24-(temperature=34°C) 48-(t=36°C) and 72-hour-(t=36°C) recordings post CA.

Conclusions: In paediatric CA patients, blinded SSEPs did not accurately predict neurological outcome in one patient. Temperature of the patient and timing of the SSEP did not affect prognostic accuracy. Further evaluation of SSEP utility in a larger cohort is required.

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Background

Accurate prediction of neurological 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].

SSEPs are well described and recommended to predicting poor outcome in adults post CA ~~and bilaterally absent N20 potentials~~[2-3]. In 2014 previous practice parameters were updated to reflect changes in CA management (therapeutic hypothermia (TH)), advances in diagnostic imaging, such as Electroencephalography and Magnetic resonance imaging (EEG, MRI) and address limitations in prognostic studies (self-fulfilling prophecy bias in unblinded studies). Bilateral absence of N20 potentials still ~~have~~ have high specificity (>90%) and a false positive rate (FPR) between 0-3% [~~42-13~~], with slightly higher FPRs in those treated with TH [5-6]. ~~but~~ However, a r~~r~~ecent ~~research~~ systematic ~~suggests~~review suggested that false positive rates may be up to ten times higher than previously thought [Amorim et al, 2018]. Because paediatric cohorts were excluded from the review, we are still unsure as to what the false positive rate is in paediatric prognostic SSEPs~~.~~

Currently SSEPs performed >72 hours post CA are used as part of multimodal prognostic algorithms but there is still a lack of blinded research in this field, [7-9] and it is difficult to apply current guidelines and recommendations to paediatric practice because the evidence cited largely excludes those <16 years of age [4, 9-11]. Whilst test accuracy is similar in paediatrics [12] caution is advised when predicting poor outcome because awakening can occur despite bilaterally absent N20 cortical potentials [13].~~.~~

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SSEPs ~~They~~ 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 travelling to the contralateral post-central gyrus/somatosensory cortex [14]. Electrographically, this is represented as a negative deflection occurring 20ms (N20) after upper limb stimulation and 35ms (N35) in lower limbs. If bilaterally absent, in the presence of peripheral and spinal potentials, severe neurological injury is indicated [14]. Although there is concern that low false positive rates and high-test specificity may be exaggerated due to unblinded studies, guidelines recommend their use when predicting poor outcome in comatose CA survivors [~~5-6, 10, 13~~4, 9-11].

Despite this, prognostic SSEPs are not considered an essential investigation in all UK intensive care units (ICU) and MRI or EEG is more commonly used [15]. Perhaps because SSEP testing requires expertise in implementation and interpretation, which is not available nationally, and the moderate interobserver variation (IOV) amongst experts when interpreting the N20 as absent [16-18]. 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^{o}C) or <72 hours post CA, a finding more frequently reported in the paediatric age range [8, 19-22]. 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 (ROSC) [610]; however, early prognosis is preferred as decisions regarding withdrawal of life sustaining therapy may already be firmly established at 72 hours post CA and thus for SSEPs to be beneficial in the paediatric intensive care setting they must be reliable early and during TTM. Several studies report on the reliability

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of SSEP performed during TTM (33-34°C) [23-26,] but current opinion suggests SSEPs should only be performed >72 hours after ROSC if treated with TTM (33-34°C) [46]. The objective of this study was to assess whether blinded SSEPs could accurately predict neurological outcome 30 days post ~~cardiac arrest (~~CA~~)~~ in children and whether TTM (33-34°C) or the timing of the SSEP test affected its prognostic accuracy.

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Methods

This single centre prospective cohort study was performed in a tertiary paediatric ICU (PICU) in the UK. Patients included were aged between 0 – 15 years, admitted to PICU following CA with cardiopulmonary resuscitation (CPR) duration greater than three minutes and remained comatose. Patients were excluded due to 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 pre-existing 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, UK [REC REF no. 13/WM/0123].

Standard post cardiac arrest management during part of the study recruitment period (2013-2014) included TTM, utilising a core temperature of 33-34°C for 24 hours with active re-warming over 16 hours to 37-37.5°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.

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Serial SSEPs were recorded in line with published guidelines [27], with the exception of recording a far field subcortical potential, at 24, 48 and 72 hours post-CA by stimulating the Median nerve aspect of the wrist or elbow and recording cortical evoked potentials (EP) from C3' and C4' (located 2cm posterior to C3/4 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, 2-3cm 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 2.1Hz. Stimulus duration was 0.2 – 0.5ms, set at an intensity 1.5 times higher than motor threshold, or at 25mA if neuromuscular junction blocking agents were administered. Two sets of 150 summated evoked potentials were recorded within 3Hz and 3KHz low and high frequency filers using either Medelec Synergy (Viasys, Woking, UK) or Myoquick matrix line (Micromed, Working, UK) recording software.

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SSEPs were analysed by one Consultant Clinical Neurophysiologist (LN) 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 blinded to all patient details except limb length and core temperature. PICU staff were blinded to SSEP results.

Neurodevelopmental and survival outcome was assessed by one ~~trainee~~ assessor (TR) using the Paediatric Cerebral Performance Category (PCPC) scale [28] 30 days after CA either via face-to-

face or telephone interviews with parent/guardian. PCPC is a 6-point scale (1- normal, 2- mild disability, 3- moderate disability, 4- severe disability, 5- coma or vegetative state, 6- death) and primary outcome was poor neurodevelopmental outcome (PCPC 4-6).

Secondary ~~outcomes~~ questions were whether~~if~~ the presence of~~present~~ SSEPs predicted good neurodevelopmental outcome (PCPC 1-3) and the effect SSEP timing and TTM (33-34°C) had on the SSEP. 24-hour SSEPs were performed during TTM (33-34°C), 48-hour during the re-warming phase, and 72-hour when normothermic.

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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 variables [29] (age, sex, location of arrest, first monitored cardiac arrhythmia, time to return of spontaneous circulation (ROSC)) were collected for each patient.

Statistical analysis

Basic summary statistics are reported for the entire study population. Binary and categorical variables are summarised using numbers and percentages. Continuous variables are summarised using mean and standard deviation (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, we formed a 2x2 table of outcome against prediction. From this table, we calculated sensitivity (true positive rate), specificity (true negative rate), positive predicted value, negative predicted value, and rates of type I and II error. The combination of these measures allows us to provide some description of the possible prognostic accuracy of SSEP. Paired t-tests were used to

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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 during their care (24, 48, 72 hours). A *p* value <0.05 was considered significant. ~~Descriptive statistics were analysed according to their distribution. Normally distributed, continuous data was reported as mean and standard deviations (SD). Non-parametric data was reported as median and interquartile ranges (IQR). Discrete data was expressed as a percentage. Sensitivity, specificity, predictive values and rates of type I and II error were calculated to estimate SSEP prognostic accuracy and Fisher's exact test analysed the significance of differences in proportions. *P* values <0.05 and <0.01 were considered significant and marked with * and ** in tables, respectively.~~ A binomial approximation was made when calculating 95% confidence intervals (CI) for the predictive measures. ~~were calculated using the binomial distribution of proportions and A~~all analysis was performed using Minitab 17.

Results

Between August 2013 – December 2014, 18 patients were admitted to PICU following CA, 16 met inclusion criteria (as two had CPR ~~CA~~ <3 minutes following CA) and 12 (75%) were successfully recruited. The families (*n*=3) and lead Consultant's lack of consent (*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) (83%). Five (42%) patients had poor outcome (PCPC 4-6), of which four (33%) died and one was moderately disabled 30 days post CA. Cause of death was hypoxic ischaemic injury following CA in all patients. Ventricular fibrillation (33%) and asystole (33%) were the most

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common presenting rhythms. Seven (58%) patients survived, three (33%) with good outcome (PCPC-1), three (33%) with minor disabilities and one (8%) with moderate disability (PCPC-3).

Median time from CA onset to first, second and third SSEP recordings were 25 hours (IQR: 24.3 -28.0), 48 hours (IQR: 46.6– 50.8) and 73 hours (IQR: 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 re-warming and 36.7°C (SD 0.4) when normothermic.

68 SSEPs (34 from left limb stimulation, 34 from right limb) were recorded in 12 patients: 20 during TTM (33-34°C), 20 during re-warming and 28 whilst normothermic (36.5-37.5°C). Progressively more SSEPs were available for analysis over serial recordings [*Table* 2] for two reasons: a change in PICU practice meant TTM (33-34°C) was not administered in two patients and artefact contamination appeared more problematic in 24- and 48-hour recordings, thus 13 SSEPs (recorded in 3 patients) were deemed indeterminate during TTM (33-34°C) (*n*= 6), re-warming (*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 analysed in 24-, 48- and 72-hour groups, respectively [*Table 2*].

An absent cortical SSEP incorrectly predicted poor outcome in one patient [*Figure 1]* (88% Specificity; 95%CI: 53%-98%) therefore the rate of false predictions was 13% (95%CI: 0%-45%) and PPV was 88% (95%CI: 45%-100%). Present cortical SSEPs correctly predicted good outcome with 100% specificity (95%CI: 51%-100%) but lower sensitivity (86%; 95%CI: 49%-

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97%). Specificity and PPV were lower in 72-hour recordings because 24- and 48-hour SSEPs of the false positive were interpreted as indeterminate due to 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 evoked potentials decreased and nerve conduction velocity (both peripheral and central) increased [*Table 4*].

Discussion

In this small prospective cohort study, ~~Blinded~~ 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 ~~utility~~accuracy. However, one patient with absent cortical potentials at 72 hours post CA had good (PCPC-3) neurological 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~~al~~ life-sustaining therapy. Although ~~W~~we ~~therefore~~ advise caution when using SSEPs in isolation to predict poor outcome in paediatric comatose CA survivors, these findings are overstated by our small sample size and conclusions must be interpreted with this in mind.

Bilaterally absent cortical SSEPs have been reported in paediatric, traumatic brain injury (TBI), CA and meningitis "good-outcome" patients [~~5-7, 10, 13,~~4,7,9-10~~,30-31~~]. These studies highlight the importance of delaying prognosis to ensure electrical interference, intraobserver variation (IOV), sedation and antiepileptics do not limit SSEP-based prognosis. However, even when

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accounted for and minimised, false positives still occur infrequently [19-22]. Absent SSEPs in paediatric CA following TBI have lower specificity in predicting poor outcome when compared to brain injury as a result of hypoxic ischaemic encephalopathy (HIE), and the presence of cortical SSEPs has a higher diagnostic odds ratio to predict awakening when compared to HIE [~~9~~13,32]. Even though a TBI patient in the present study had poor outcome correctly predicted at 24, 48 & 72 hours post CA, SSEPs performed within 24 hours of TBI should be repeated [~~11~~12] as TBI contributed to 8% [1/12 patients] of an already small sample size of study participants.

Our false positive had no known comorbidities which could explain an absent SSEP. Sedation was not excessive and not significantly altered during TTM (33-34^{o}C). Technically, the SSEP was difficult to record and deemed indeterminate at 24- & 48-hour recordings due to interference but was interpreted as absent at 72-hours (See *figure 1*).

Interpreting serial SSEPs between hypothermic (TTM (33-34^{o}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^{o}C) which raised concerns regarding the accuracy of prognostic tests performed during hypothermia [7]. Several studies addressed this issue [24-26, 30] and guidelines support SSEP prognostication at 24 hours if no TTM (33-34^{o}~~C)~~C) is used, and at 72-hours if used [~~2,~~4~~5~~-6]. Rationale for delayed prognosis was the increased rate of false predictions seen in TTM (33-34^{o}~~C)~~C) treated patients. These were attributed to excessive artefact and an increased rate of IOV. In the current study, an accurate

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prognosis was determined at 24-hours in the majority (66%) of patients. However, exclusion of SSEP traces due to excessive artefact was highest in the 24-hour group (n=6) in comparison to the 48- (n= 5) and 72-hour (n=2) group. During rewarming, increasing body temperature was associated with decreasing latency of evoked potentials and increase in peripheral and central nerve conduction velocity in keeping with previous studies [23]. The lack of statistical significance could be due to small sample size.

There are ~~potential~~ limitations to the study. First, IOV was not formally assessed and has been described as moderate to substantial when interpreting prognostic SSEPs [16-18] and should be addressed in future studies. Secondly, PCPC is a simple and reliable measure of neurodevelopmental outcome and is commonly used in paediatric cardiac arrest studies (28, 34); however, the broad categories may limit its ability to accurately differentiate good and poor outcome. There remains disagreement as to whether PCPC 1-2 or 1-3 demonstrates a good outcome and whether PCPC 4 is good/poor outcome [~~9~~13, 35-40]. Median age of children assessed with PCPC is 3 years [28] and uses school-based and age-specific criteria to assess good outcome (PCPC 1-3). 33% of our cohort were neonates (one of which had outcome falsely predicted) and making the distinction between good and bad outcome categories was challenging. Confidence intervals for proportional estimates are wide (48% - 100%), indicating we have little knowledge of the true prognostic accuracy of SSEPs in this cohort. Recruiting more patients would help clarify this and thus large blinded prospective studies are still required.

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Unblinded~~Pr~~ prognostic SSEPs in adult and paediatric HIE studies are close to 100% specific when prognosticating poor outcome after coma [2-12]. In paediatric age (>30 days - <19 years), 97% of patients with absent SSEPs and 92% of patients with present SSEPs have outcome predicted correctly [~~9~~13] which is similar to presented findings. Sensitivity is low in adults (45-48%) [~~5~~4] and paediatrics (70-80%) [~~9~~13, 32] because present cortical responses do not ensure good outcome [41]. Sensit~~i~~ivity in paediatrics -may be higher due to infant brain plasticity and the marked difference in favourable ICU prognosis in comparison to adults [~~9~~13]. 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, heterogenous 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 emphasise that findings are ~~overstated~~likely due to small sample size. ~~despite a small, heterogeneous sample, and w~~We believe the current findings add to the clinical utility of prognostic SSEPs~~. However~~ and multimodal approaches to CA coma prognostication are essential in order to minimise the risk of making false predictions.

Accurate prognosis of comatose CA children is challenging and false positive SSEP results can occur. Our study supports the utility of SSEPs to predict favourable and unfavourable neurological 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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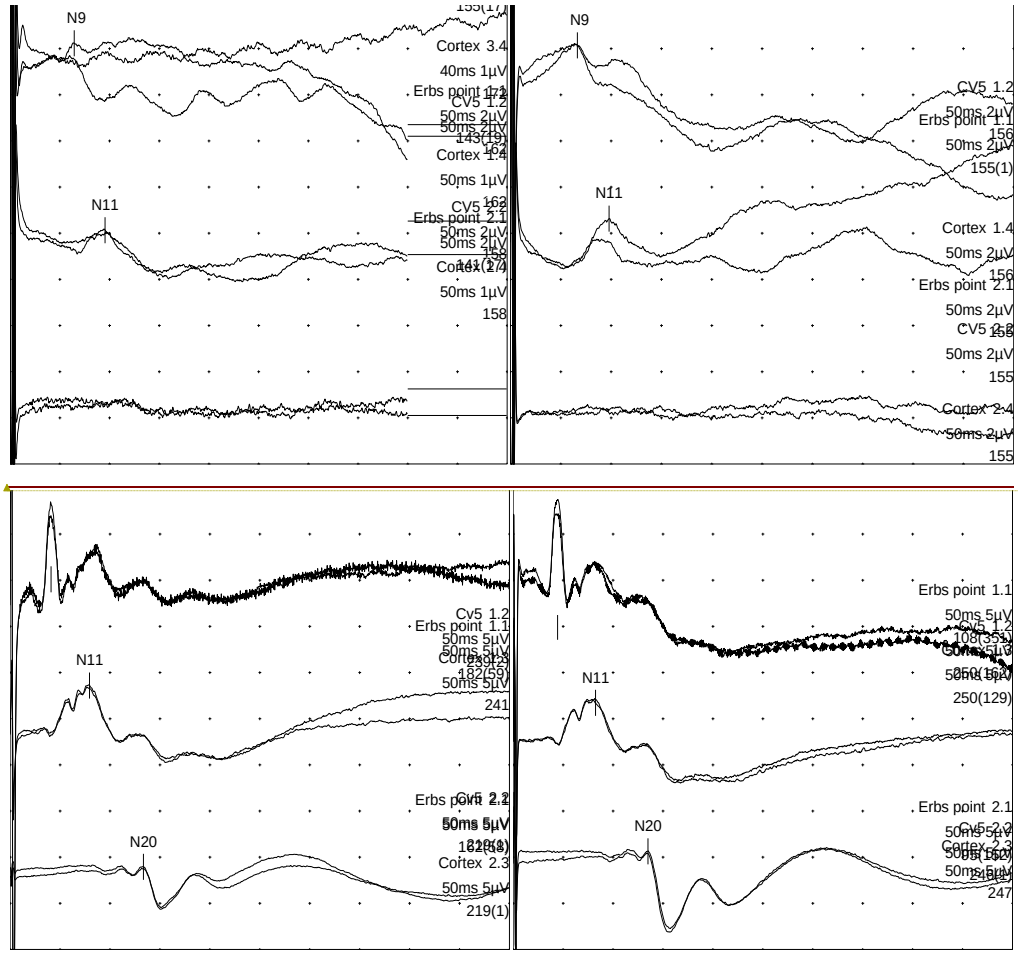
FIGURES



~~Figure 1: 72-hour right and left limb SSEPs interpreted as bilaterally absent in a patient with good neurological recovery (PCPC- 3) 30 days post CA. Peripheral, spinal and cortical waveforms displayed in top, middle and bottom lines, respectively~~

Figure 1: Top: 72-hour right and left limb SSEPs interpreted as bilaterally absent in a patient with good outcome (PCPC- 3) 30 days post CA. Bottom: 72 hour right and left limb SSEPs interpreted as bilaterally present in a patient with good outcome (PCPC) Present peripheral, spinal and cortical (PCPC- 1). Peripheral, spinal and

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Tables

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 (16)
Location of Cardiac Arrest (n%)	
➢ **In-hospital**	3 (25)
➢ **Out-of-Hospital**	9 (75)
TTM (33-34^{o}C) use, n (%)	10 (83)
ROSC, mins, 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)

Table 1: Demographics and resuscitation factors of the 12 patients recruited: VF – Ventricular fibrillation, CA – Cardiac arrest, PEA – Pulseless electrical activity, IQR- Interquartile range, CPR – Cardiopulmonary resuscitation; TTM – Targeted Temperature Management, ROSC- Return of spontaneous circulation, PCPC- Paediatric Cerebral Performance Category scale.

Participant	Interpretation of SSEP						Outcome / PCPC Score	
	24 Hour		48 Hour		72 Hour			
	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.	Present	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								
Left/Right	8	8	9	10	9	11	26	29
Total	16		19		20		55	

Table 2: Interpretation of serial SSEPs performed after left and right-limb stimulation and 30 day outcome assessed via PCPC score. Total SSEPs recorded from left and right limbs over serial recordings detailed separately. N/A: Not performed and patient did not receive TTM; Ind: Indeterminate SSEP.

Predictive power calculations	Absent cortical SSEPs			Present cortical SSEPs
Time	**24 Hour, ****	**48 Hour, ****	**72 Hour, ***	**72 Hour, ****
Temperature ^{o}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 to 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

Table 3: Predictive power of absent and present cortical SSEPs at 24, 48 and 72 hours post cardiac arrest. SD- Standard deviation, CI- Confidence interval, PPV- Positive predictive value, NPV- Negative predictive value, FPR- False positive rate** ~~*p*=<0.01, * *p*= <0.05~~

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Core temperature, Mean (±SD)	Peak onset latency, ms 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)

Table 4: Combined left and right peak onset latency of peripheral, spinal and cortical evoked potentials following median nerve stimulation at the wrist; peripheral and central nerve conduction velocities.* $p<0.05$