Enhanced analysis of somatosensory evoked potentials at 20–30 milliseconds can predict neurological outcome after cardiac arrest

Gourd, Nicholas M.; Bigham, Colin; Broomfield, Nicola; Nye, Lucy; Stapleton, Liana; Stead, Emma; Smith, Andrew; Baker, Amy; Chynoweth, Jade; Hosking, Joanne; Hudson, Nigel; Nikitas, Nikitas

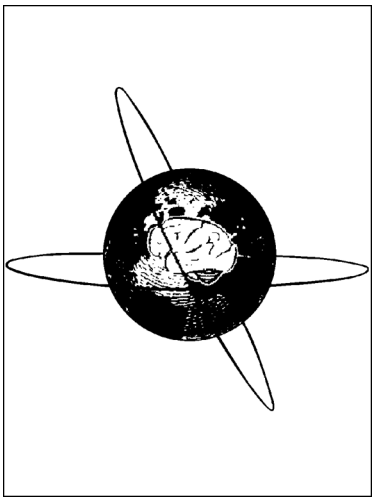
Published in:
Clinical Neurophysiology

DOI:
10.1016/j.clinph.2023.06.020

Publication date:
2023

Document version:
Peer reviewed version

Journal Pre-proofs



Enhanced analysis of Somatosensory Evoked Potentials at 20-30 milliseconds can predict neurological outcome after cardiac arrest

Nicholas M Gourd, Colin Bigham, Nicola Broomfield, Lucy Nye, Liana Stapleton, Emma Stead, Andrew Smith, Amy Baker, Jade Chynoweth, Joanne Hosking, Nigel Hudson, Nikitas Nikitas

PII: S1388-2457(23)00675-2
DOI: https://doi.org/10.1016/j.clinph.2023.06.020
Reference: CLINPH 2010237

To appear in: *Clinical Neurophysiology*

Received Date: 19 December 2022
Revised Date: 12 June 2023
Accepted Date: 17 June 2023

Please cite this article as: Gourd, N.M., Bigham, C., Broomfield, N., Nye, L., Stapleton, L., Stead, E., Smith, A., Baker, A., Chynoweth, J., Hosking, J., Hudson, N., Nikitas, N., Enhanced analysis of Somatosensory Evoked Potentials at 20-30 milliseconds can predict neurological outcome after cardiac arrest, *Clinical Neurophysiology* (2023), doi: https://doi.org/10.1016/j.clinph.2023.06.020

Enhanced analysis of Somatosensory Evoked Potentials at 20-30 milliseconds can predict neurological outcome after cardiac arrest

Dr Nicholas M Gourd BMBS, Foundation years doctor, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Dr Colin Bigham, Consultant in Intensive Care Medicine, Department of Intensive Care Medicine, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Mrs Nicola Broomfield, Clinical Scientist, Lead of the Neurophysiology, Department of Neurophysiology, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Mrs Lucy Nye, Clinical Physiologist, Department of Neurophysiology, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Miss Liana Stapleton, Intensive Care Senior Research Nurse, Department of Intensive Care Medicine, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Miss Emma Stead, Clinical Scientist, Department of Neurophysiology, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Mr Andrew Smith, Clinical Physiologist, Department of Neurophysiology, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Amy Baker, Senior Research Fellow in Medical Statistics, Peninsula Medical School (Faculty of Health), University of Plymouth UK.

Jade Chynoweth, Research Assistant in Medical Statistics, Peninsula Medical School (Faculty of Health), University of Plymouth UK.

Joanne Hosking, Senior Research Fellow & BMBS Lead for Statistics & Numeracy, Peninsula Medical School (Faculty of Health), University of Plymouth UK.

Mr Nigel Hudson, Clinical Physiologist, Department of Neurophysiology, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK.

Dr Nikitas Nikitas MD PhD, Consultant in Intensive Care Medicine, Department of Intensive Care Medicine, University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth UK. Honorary Clinical Lecturer, Peninsula Medical School (Faculty of Health), University of Plymouth UK.

Corresponding author:

Nikitas Nikitas

E-mail: nikitas.nikitas@nhs.net

Institution where the work was performed: University Hospitals Plymouth NHS Trust, Derriford Hospital, Plymouth, United Kingdom.

Highlights

-P25/30 demonstrated higher Positive Predictive Value than the used in clinical practice N20

-Analysis of Peak To Trough amplitude of 20-30msec complex achieved the highest prognostic efficacy and interpreters agreement

-Using amplitude size in analysis, standardised waveform interpretation and improved the predictive value of 20-30msec complex

Abstract

Objective

This study attempted to test the effectiveness of an enhanced analysis of the 20-30msec complex of somatosensory evoked potentials, in predicting the short-term outcome of comatose survivors of out of hospital cardiac arrest and compare it with the current clinical practice.

Methods

Single-centre, prospective, observational study. Median nerve SSEP recording performed at 24-36 hours post-return of spontaneous circulation. Recording was analysed using amplitude measurements of P25/30 and Peak-To-Trough of 20-30msec complex and thresholds to decide P25/30 presence. Neurological outcome was dichotomised into favourable and unfavourable.

Results

89 participants were analysed. 43.8% had favourable and 56.2% unfavourable outcome. The sensitivity, specificity, positive and negative predictive values of the present SSEP and favourable outcome were calculated. P25/30 presence and size of PTT improved positive predictive value and specificity, while maintained similar negative predictive value and sensitivity, compared to the current practice. Inter-interpreter agreement was also improved.

Conclusions

Enhanced analysis of the SSEP at 20-30millisecond complex could improve the short-term prognostic accuracy for short-term neurological outcome in comatose survivors of cardiac arrest.

Significance

Peak-To-Trough analysis of the 20-30msec SSEP waveform appears to be the best predictor of neurological outcome following out of hospital cardiac arrest. It is also the easiest and most reliable to analyse.

Keywords: Somatosensory evoked potential, P25/30, N20, cardiac arrest, outcome, neuro-prognostication.

1. Introduction

The high mortality rate and high chance of unfavourable outcome among survivors of out of hospital cardiac arrest (OHCA) is due to the hypoxic-ischaemic brain injury (HIBI) (Witten et al, 2019). HIBI is thought to be a consequence of a two-stage process, an ischaemic stage during the period of no cardiac output, followed by a reperfusion stage during successful resuscitation (Sekhon et al, 2017).

Clinically confirmed by a multimodal approach, HIBI-induced unfavourable outcome is the main factor affecting the decision for withdrawal of life sustaining treatment (WLST) (Resuscitation council, 2021).

Being able to predict the favourable or unfavourable outcomes in survivors of OHCA can serve multiple purposes like improved decision making and prevention of unnecessary continuation of futile treatment, clarity for families and realistic management of their expectations. However, reliable neuro-prognostication remains a challenging task, despite the development of multiple useful tools. One of the most important tools to deal with this clinical uncertainty is the somatosensory evoked potentials (SSEP). SSEP are recorded electrical waveforms originating from the somatosensory cerebral cortex in response to a peripheral stimulus.

In current clinical practice across the UK and other countries, the presence or absence of the SSEP is based on a qualitative interpretation of the waveform. The qualitative assessment involves a neurophysiologist observing the presence of a deflection above or below an electrical baseline. N20 (upward deflection recorded 20msec after peripheral stimulation) is the current SSEP “component” used for neuro-prognostication. The bilateral absence of the N20 is strongly predictive of an unfavourable outcome (Sandroni et al, 2013), however the presence (unilateral or bilateral) of the N20 does not strongly predict a favourable outcome. The latter represents the principal drawback of the clinical application of N20 SSEP (Figure 1a).

Methodological aspects of the N20 interpretation could also contribute to its limitations: (i) There are difficulties in defining the electrical baseline of the recording due to variable degrees of extracerebral noise interfering with the recording, (ii) The definition of the presence or absence of an N20 waveform could vary from operator to operator.

To deal with the low positive predictive value of N20 for a favourable outcome, this study chose to additionally analyse an alternative SSEP: the P25/30, a downward deflection which is recorded on both sides of the brain cortex immediately post N20 at 25-30msec after a peripheral stimulus. N20 originates from the primary somatosensory cortex in the posterior bank of the Rolandic fissure representing Brodmann’s area 3b in the parietal lobe. P25/30 originates also in the primary somatosensory cortex but in the Brodmann’s area 1. P25/30 is recorded from the cortex near the central sulcus and the central scalp, N20 is recorded from the somatosensory cortex and parietal scalp, P25/30 is a radial dipole while N20 is a tangential dipole of the primary somatosensory cortex (Allison et al, 1991).

The choice of P25/30 as an SSEP in this study was based on the following factors: i) cumulative evidence before this study had been suggestive that the P25/30 could potentially be associated with improved prognostic performance in survivors of cardiac arrest (Kim et al, 2018; Oh et al, 2019; Van Soest et al, 2021), ii) the point of origin of

P25/30 is different to that of N20 and thus can be assessed as a distinct SSEP (Allison et al, 1991), iii) due to its very close proximity on the recording – the P25/30 is practically the continuation of the N20 waveform – the two SSEPs can be interpreted as one, "the 20-30msec complex", iv) analysis of "20-30msec SSEP complex" can also be undertaken as the direct manual measurement of the amplitude of Peak to Trough (PTT) of the 20-30msec complex.

This study assessed whether the interpretation of the presence or absence of the P25/30, could increase the prognostic accuracy of SSEP beyond that of N20 in survivors of out of hospital cardiac arrest. This was attempted both by interpreting the P25/30 as a single SSEP and in combination with N20 in the 20-30msec complex.

(Figure 1b and Figure 1c).

2. METHODS

2.1 Study design

This was a single-centre, prospective, observational, study of the 20-30msec SSEP complex (both P25/30 and PTT) and its correlation with the favourable and unfavourable outcome in comatose survivors of OHCA, conducted over 3 years (September 2018 – September 2021). Ethical approval of the study was granted by North-West – Haydock Research Ethics Committee [REC reference: 18/NW/0623] The study was conducted in full conformity with relevant regulations and with UK policy framework for health and social care research (2017), which have their basis in the declaration of Helsinki.

2.2 Screening and Enrolment

Adult (≥ 18 years old) comatose survivors of OHCA, who were admitted to a single UK tertiary intensive care unit (ICU) were enrolled. The inclusion and exclusion criteria are presented in Table 1.

Within the first 24 hours in ICU, eligible patients were screened and enrolled to the study after written informed consent was granted by the participant's next of kin. Additional participant written informed consent was granted by those participants who recovered and regained mental capacity.

2.3 ICU management

All participants of the study were treated following national and local clinical guidelines. Principle elements included:

(i) Ventilatory, cardiovascular or renal support as required, (ii) targeted temperature management (TTM) with external cooling device (Arctic Sun™ 5000 TTM system/ArcticGel™ Pads). For 24 hours following return of spontaneous circulation (ROSC), mean patient's temperature (T) was maintained at 36ºC and for the next 48 hours (up to 72 hours) T was maintained between 36-37ºC. Patients regaining

consciousness with Glasgow Coma Scale (GCS) motor response of 6 (M6), between 36 and 72 hours post ROSC, had their TTM discontinued prior to 72 hours post ROSC, (iii) treatment of the underlying cause of cardiac arrest, (iv) achievement of other neuroprotective targets (head elevation at ≥ 30°, PaO2 > 9kPa, PaCO2 4.5-6kPa, Glu 6-10mmol/L, MAP > 65 at tragus), (vi) deep sedation [Richmond-Agitation-Sedation Score (RASS) of -4 to -5] for the first 24-36 hours post ROSC.

2.4 SSEP recording

Between 24 hours to 36 hours post ROSC, the SSEP recording was performed on all participants. All participants were sedated, and their T was 36°C. A neuromuscular blocking agent (atracurium or rocuronium) was allowed in some cases during the SSEP recording to achieve optimal recording quality. Figure 2 presents the SSEP recording protocol (full details in Supplementary Material, pages 1-3). It is clarified that a total of at least 2 trial runs with 500 averages per trial was performed; the grand average of the 2 runs was taken for the final amplitude measurement. All measurements were recorded in microvolts and are measured at a screen value of 1microvolt per division.

2.5 SSEP interpretation

Anonymised SSEP recordings were analysed by two interpreters independently (neurophysiology clinical scientists). They were blinded to each other's assessment and all patient details and outcomes. Interpretation included qualitative assessments (visual presence or absence of N20 or P25/30) and quantitative assessments (manual measurement of the size of the amplitude of the evoked potential from a defined baseline). Specifically, the quantitative assessments required manual measurements [in microvolts (μV)] of deviations from a baseline for P25/30 and N20 waves and manual measurement [in μV] of the amplitude of the peak to trough of the entire 20-30 complex. In a consistently followed approach, the baseline was defined as the most stable point of each trace (part of the trace with least interference and most horizontal area before waveform was visible). This was to be used as the starting point for all further SSEP amplitude measurements to be taken. Once the measurements had been performed, then: (i) presence or absence of P25/30 was assigned, based on a chosen amplitude threshold, (ii) presence and absence of N20 was assigned based on a chosen amplitude threshold, (iii) the amplitude of the Peak to Trough (PTT) of 20-30 msec SSEP complex was recorded (Figure 3).

Any discrepancy between the two interpretations required a third interpreter to provide the definitive results for the study. The third interpreter was also blinded to prior results and patient details.

SSEP recordings usually demonstrate differing amplitudes in the two cerebral hemispheres. The waveform results from the cerebral hemisphere with the larger amplitudes were those used in study interpretation (including when in hemisphere the 20-30 msec complex was absent).

The results of the above quantitative interpretation (P25/30 presence or absence and the size of Peak To Trough [PTT]) and their correlation with the short-term outcome of the participants were compared to the ones of the qualitative N20 interpretation.

The results of the bedside visual interpretation of N20 were disclosed to the clinicians as is normal practice. Any other results, or interpretations of the SSEP waveform (including study quantitative SSEP interpretation and analysis) were not disclosed to any member of the ICU clinical team. In that way, the study results did not affect clinicians' decision making.

2.6 Threshold measurement of N20 and P25/30 amplitude

The baseline was defined as the most stable point of each trace. It had the least interference and most horizontal segments prior to the 20-30msec waveform. Peak amplitude measurements were taken from this baseline. Two different amplitudes were chosen as thresholds to dichotomise the 20-30msec SSEP waveform into present or absent: 0.5μV and 0.2 μV. When the SSEP amplitude was lower than the chosen threshold, the SSEP was considered absent. When the SSEP amplitude was equal to/higher than the chosen threshold the SSEP was considered present (Figure 3 and Figure 4). The choice of two thresholds (0.2μV and 0.5μV) for N20 and P25/30 was to analyse how a higher and lower threshold could impact on prognostic performance.

2.7 Peak to Trough (PTT) of the 20-30msec complex

Amplitudes of the Peak To Trough (PTT) of the 20-30msec SSEP complex were measured without requiring baseline determination. As PTT is a novel measurement with insufficient evidence for amplitude thresholds linked to prognosis, microvolt-prognosis correlations were explored as part of the analysis (Figure 1b, Figure 3 and Figure 4).

2.8 Follow Up

Each participant was followed to hospital discharge or death, whichever occurred first. To ensure an accurate neurological assessment, the patient needed to be off sedation for an adequate length of time and the presence of non-neurological factors (like hypoxia, hypercapnia, significant cardiovascular instability, uraemia, and acidosis) had been ruled out. If the above criteria were met, then cerebral performance category (CPC) score (Table 2) was assessed within the last 24 hours prior to their hospital discharge or death.

One participant unfortunately developed an unrelated catastrophic event whilst still in hospital, having had full neurological recovery prior to that. The participant was considered to have made a full neurological recovery for the trial data analysis. The list of the clinical data which were collected prospectively is shown in Supplementary Material, pages 3-4.

2.9 Statistics

Demographic information of participants was summarised using descriptive statistics.

Continuous measures were summarised as means, standard deviations and ranges where the distribution appears normal, and as medians, inter-quartile ranges and ranges otherwise. Categorical data were summarised by frequencies and percentages.

The primary outcome measure was the CPC score at hospital discharge with discrete values ranging from 1 to 5. The score was dichotomised as 1-2 (favourable outcome) and 3-5 (unfavourable outcome).

Sensitivity, specificity, and predictive values of P25/30, N20 and PTT 20-30 msec SSEP complex for predicting favourable and unfavourable outcome were computed.

Counts and percentages were presented for each categorical variable by outcome and overall. Chi-squared tests were used to assess the association between outcome and each demographic and clinical variable.

Where appropriate, parameter estimates were presented with 95% confidence intervals. No interim analysis was performed. Whenever applicable, a 5% level of significance was used.

Receiver operating characteristic (ROC) curves were presented to illustrate the prognostic performance of the three analysed SSEP waveforms (P25/30, PTT of the 20-30 msec complex and N20).

3. RESULTS

One hundred and twenty-nine comatose survivors of OHCA were admitted and screened during the study period. Thirty-six out of the 129 admitted survivors of OHCA were not enrolled due to either meeting exclusion criteria, treating clinician decision or technical issues with recording. Ninety-three participants were enrolled to the study. None of the participants was requested to be withdrawn from the study after their initial enrolment. Finally, 89 participants were included in the analysis as reliable assessment of the CPC score was not possible in 4 of the 93 participants (Figure 5).

For the 89 participants, the clinical results are presented in Table 3.

43.8% of the participants had a favourable outcome and 56.2% had an unfavourable outcome at hospital discharge.

The mortality at hospital discharge was 98.0% in the participants with an unfavourable outcome compared to 2.6% (one participant) in those with a favourable outcome. Death occurred within a mean period of 7.63 days after ROSC in the participants with unfavourable outcome.

The mean time of SSEP recording post ROSC was 25.2 hours in the participants with favourable outcome and 26.3h in those with unfavourable outcome.

There was no difference in mean temperature (36.1^{o}C), admission physiological parameters, prior performance status (Charlson Comorbidity Index (CCI) and WHO preadmission performance status) or time from ROSC to ICU admission in those with favourable or unfavourable outcomes. (CCI and WHO performance status can be seen in Supplementary Material, pages 10-11.) Those patients who progressed to unfavourable outcomes were more likely to have a non-cardiac aetiology of OHCA, and an abnormal CT head on admission.

3.1 Amplitude of P25/30 and N20 as a prognostic marker: presence threshold ≥ 0.5μV from baseline

The positive predictive value (PPV) and negative predictive value (NPV) of a present P25/30 predicting a favourable outcome were: PPV 81.82% (95% confidence interval [CI] 73.81-89.23), NPV 93.33% (95% CI 88.15-98.51) with a sensitivity of 92.31% (95% CI 86.77-97.85) and specificity of 84.00% (95% CI 76.38-91.62).

The PPV and NPV of a present N20 predicting a favourable outcome were: PPV 89.74% (95% CI 83.44-96.04), NPV 92.00% (95% CI 86.36-97.64), with a sensitivity of 89.74% (95% CI 83.44-96.04) and specificity of 92.00% (95% CI 86.36-97.64).

This means that unfortunately, when an amplitude threshold of 0.5μV was used to define a presence/absence of the P25/30 or N20, the NPV was reduced from 100%. In other words, there were study patients with absent SSEP waveforms (by the microvolts definition) that had favourable outcomes. This later concern would trouble clinicians looking for certainty with the clinical decision-making including decision for palliation.

3.2 Amplitude of P25/30 and N20 as a prognostic marker: presence threshold ≥ 0.2μV from baseline

The PPV and NPV of a present P25/30 predicting a favourable outcome were: PPV 73.58% (95% CI 64.42-82.74), NPV 100%, with a sensitivity of 100% and specificity of 72.00% (95% CI 62.67-81.33).

The PPV and NPV of a present N20 predicting a favourable outcome were: PPV 67.24% (95% CI 57.49-76.99), NPV 100%, with a sensitivity of 100% and specificity of 62.00% (95% CI 51.92-72.08).

At this threshold, PPV of present P25/30 was slightly superior to the PPV of the N20 for a favourable outcome. Reassuringly, no participants with absent P25/30 or absent N20s had a favourable outcome. PPV using quantitative interpretation of presence/absence of SSEP was better than the PPV achieved during qualitative interpretation of SSEP (see section 3.4). This could potentially favour amplitude assessment as a preferred routine analysing method.

3.3 Peak To Trough (PTT) of the 20-30msec SSEP complex. Correlating size of PTT to favourable and unfavourable outcomes

We aimed to determine a threshold that ensured 100% NPV and maximised favourable outcome predictions. A range of amplitude thresholds from 0.1μV to 2.0μV were tested. The optimal threshold amplitude which maintained the 100% NPV and maximised the PPV for favourable outcome was 0.6μV.

Assessing the correlation of PTT size with the outcome, analysis using 0.6μV as threshold showed: PPV 80% (95% CI 71.22-87.96), NPV 100%, with a sensitivity of 100% and a specificity of 80.00% (95% CI 71.69-88.31). No dichotomised approach of presence/absence of SSEP was necessary when PTT was analysed during the quantitative interpretation. PTT < 0.6 μV predicted the unfavourable outcome reliably whilst a PTT ≥ 0.6 μV had predicted the favourable outcome in 79.59% of the study participants. This contrasted with 74% and 67% PPV for P25/30 and N20 respectively (at 0.2μV).

Generally, PTT interpretation was also easier to perform (without need for definition of baseline for amplitude measurement) and more reliable (demonstrating 100% inter-interpreter agreement with no need for a third interpreter).

3.4 Comparison of P25/30 and PTT with the qualitative interpretation of N20

In daily clinical practice, interpreting presence, or absence of the N20 is by inspection of the recording (qualitative interpretation). The amplitude of the N20 is not measured and the definition of presence and absence of the SSEP against the baseline is not consistently standardised between different interpreters and different centres in a reproducible way.

The PPV and the NPV of a qualitatively present N20 indicating a favourable outcome were PPV 62.90% (95%CI 52.86-72.94) and NPV 100%, with a Sensitivity of 100% and Specificity of 54.00% (95% CI 43.65-64.35). This finding suggested that qualitative interpretation of N20 demonstrated lower PPV as compared against all quantitative P25/30 and N20 results and the PTT analysis.

The comparative presentation of PPV, NPV, sensitivity and specificity of the quantitative interpretation of P25/30 and PTT against the qualitative interpretation of N20 (current clinical practice) is shown on Table 4 and Figure 6.

The ROC curves for P25/30 using 0.2 μV as threshold, for PTT using a cut-off amplitude of 0.6μV and for the current clinical practice are shown in Figure 7. The area under curve for P25/30 was 0.9749, compared with 0.9774 for PTT and 0.8351 for qualitative N20 interpretation.

(Additional, raw, data of the results can be found in the Supplementary Material, pages 5-9.)

4. Discussion

As part of current standards of care, qualitative interpretation of the N20 SSEP more than 24 hours post ROSC is an integral component of the current multi-modal approach to neuro-prognostication in comatose survivors of OHCA (Resuscitation council, 2021). Current analysis of the N20 waveform is a visual assessment.

In this study, we have analysed (i) a quantification of SSEP interpretation beyond visual assessments and (ii) extended the analysis of the waveform beyond the N20 wave into the wider 20-30msec complex. This is with the aim of improving the accuracy and reliability of detecting of favourable and unfavourable outcomes.

With regards to increasing the reliability of the SSEP waveform analysis: it was confirmed once again that it is possible to assign baselines to the waveform and to measure the amplitudes of the two waveforms making up the 20-30msec complex (N20 and P25/30). We also used a method of measuring from the peak of the N20 to the trough of the P25/30, without need to consider the baseline. This method was clearly the easiest to measure and produced the best inter-interpreter reliability.

With regards to improving accuracy of prognosis following OHCA, quantitative analysis of the Peak to Trough (PTT) of the entire 20-30msec complex provided the optimal accuracy in our small study. Detecting a threshold of below 0.6μV implied we could be 100% certain there would be a poor prognosis. Conversely, with an amplitude of over 0.6 μV, we could be 80% certain of a favourable short-term outcome (as compared to 63% using visually assessed N20s).

4.1 P25/30 analysis

We used either 0.2μV or 0.5μV as thresholds for defining presence/absence in our quantitative interpretation of P25/30 and N20. The findings of this study suggested potentially improved prognostic accuracy when utilising measured thresholds, as seen in other studies (Glimmerveen et al, 2020; Carrai et al, 2019; Zandbergen et al, 2006).

Other study groups have sought to define similar thresholds at which P25/30 is present. These values include, but are not limited to, 0.4μV (Glimmerveen et al, 2020), 0.62μV (Endisch et al, 2015). In our study, using a 0.5μV threshold for quantitative analysis, had the best PPV (82%), but the NPV reduced from 100%. This could have adverse implications on potential palliation decisions in clinical practice.

Previously, a single-centre retrospective observational study (Carrai et al, 2019) had like our prospective observational study sought to determine the relationship between PTT amplitude and neurological outcome. That study similarly showed improved

prognostication with a 10.9% increase in correct prediction of unfavourable outcome at an early stage post cardiac arrest, with a sensitivity of 71.8% and specificity of 100%. However, differences between the two studies were the following: i. Carrai et al study's population was slightly higher than ours (119 vs 89 analysed participants). However, our study population was more homogeneous including only survivors of out of hospital cardiac arrest. Our study had broader exclusion criteria (like traumatic cardiac arrest and haemodynamic instability) whereby for the Carrai et al study, exclusion criteria was primarily neurological (traumatic brain injury and intracerebral haemorrhage). Participants in our study were all normothermic and not a combination of normo- and hypothermic ones. In our institution WLST was an established clinical practice contrary to the prohibition of WLST in the institution where Carrai et al study was conducted, ii. Our study was designed to study only the value of 20-30msec SSEP complex in neuroprognostication and did not aim to determine the relationship between electroencephalographic patterns and SSEP amplitude, iii. We focused on a comparative analysis of the prognostic value of the quantitative interpretation of the whole 20-30msec complex (as PTT) and its individual components (P25/30 and N20) whereas Carrai et al focused only on PTT, iv. Contrary to the Carrai et al study which looked at long/mid-term (6-month) outcome using the glasgow outcome scale (GOS), our study looked only at the short-term outcome (hospital discharge) using the CPC score, vi. With regards to data analysis, in our study the amplitude of PTT was analysed for the dichotomised outcome (favourable – unfavourable) and not for each value of the prognostic score. Also, while the main aim of the Carrai et al study was to identify a level of amplitude of the PTT below which the PPV for the unfavourable outcome was 100%, our aim was to identify an amplitude threshold which was associated with the highest PPV for the favourable outcome, whilst maintaining 100% NPV for the favourable outcome.

This brief comparative analysis between two similar studies not only serves to demonstrate the multiple ways in which studies of this nature can differ, but also to highlight that, despite the differences in methods and analysis between the studies, the ability of the PTT to improve neurological prognostication remained consistently present and reproducible across different clinical and research settings.

Using quantitative analysis at a threshold of 0.2μV did not suffer from the same NPV concerns. Reassuringly, quantitative P25/30 assessment at this threshold had a higher PPV for favourable outcomes compared with visual N20 assessment (74% vs 63%). This improvement likely represents the correct interpretation of those patients whose record is corrupted by background noise. The analysis of both 0.2VμV and 0.5μV thresholds shows how a tension exists between a higher threshold at which incorrect attribution of noise as genuinely present waveforms is more likely, but also the possibility of dismissing a genuinely present waveform. The converse is seen with the lower 0.2μV threshold. This study does not seek to claim a particular threshold at which this tension is resolved, but to demonstrate the implications of setting a higher and lower threshold.

Incorporating quantitative P25/30 interpretation into clinical algorithms could be useful. This is a reassuring finding and has been noted before in other publications (Kim et al, 2018; Oh et al, 2019; Van Soest et al, 2021). However, these prior studies have been different in a variety of ways. Some have been retrospective, others have used

hypothermia, others less specific about SSEP recording times (Benghanem et al, 2022) and some have used qualitative assessments of the P25/30 complex.

4.2 Analysis of peak-to-trough of 20-30msec complex

PTT demonstrated the highest PPV and specificity for a favourable outcome (achieved with the selection of the ≥ 0.6μV cut-off amplitude) whilst maintaining a 100% NPV. It was associated with the maximum possible inter-interpreter agreement (100%). The significance of this latter observation can be contextualised by considering other studies looking at SSEP N20 recordings and inter-observer agreement. Analysis of 56 SSEP N20 recordings by 5 neurophysiologists resulted in a kappa coefficient between 0.2 and 0.65 (Zandbergen et al, 2006). A study using 4 experienced neurologists analysing 163 SSEPs had a kappa coefficient of 0.88 for recordings in patients who went on to have favourable outcome and 0.76 for recordings in patients with unfavourable outcomes (Pfeifer et al, 2013). Another study found a kappa coefficient between 0.39 to 0.79 (Hakimi et al, 2009). Developing a technique to optimise inter-observer consistency across SSEP recordings could be a significant clinical improvement.

Based on our results, we have chosen 0.6 μV as a threshold for PTT analysis. There is little data to contextualise our chosen amplitudes. The only previous study which explored whether an N20 to P25/30 amplitude cut-off could be used, found that <0.64μV was associated with unfavourable outcome, >2.31μV with favourable outcome, with values in between associated with either outcome (Oh et al, 2019). However, in that retrospective study a different methodological approach was followed: patients were treated with hypothermia, WLST was prohibited, a median time from ROSC to SSEP recording was 41.6 hours (patients who awakened at rewarming were not included in the study).

In summary, PTT of the 20-30msec complex could be a promising tool to maximise prognostic capabilities of the early SSEP waveforms. This could have positive consequences for patients and family: optimised decision making, reduced futile treatment, improved family communication. There could also be wider financial and workforce planning benefits. Intuitively, PTT analysis is associated with the following advantages: (i) it is an integrative method of analysing the entire 20-30msec complex, (ii) baseline determination is not needed (iii) the function of two crucial areas of the somatosensory cerebral cortex is involved in its production, (iv) the inter-interpreter variation could be minimised, (v) given its low dependence on interpreters' skills, the PTT amplitude could be amenable to automated measurement.

However, despite the encouraging signals, there is still much more clarification needed: (i) PTT's performance correlated to the favourable and unfavourable outcome need to be tested in large multi-centre prospective observational studies, (ii) refining optimum cut-off amplitudes that predict favourable and unfavourable outcomes is needed, (iii) the PTT need to be compared and assessed against other elements of neuro-prognostication [neuron specific enolase, electroencephalogram, brain imaging, clinical findings].

4.3 Study strengths

The strengths of this study can be summarised as follows: this was a prospective, real-life, observational study with standardisation and reproducibility of the conditions of the study conduction. The clinical management of all the patients in the study was carefully protocolised, minimising confounding clinical variables. The timings of SSEP recording and the methods used for SSEP interpretation were consistent and easily reproducible. This study provides a good structure for potential future, larger-scale, studies.

4.4 Study limitations

Despite the study being tightly protocoled and well performed, it was a relatively small single-centre study with participants' follow up limited to hospital discharge (rather than 6 months onwards). Therefore, this study's results cannot be directly compared to the results of those studies which looked at the long-term outcome.

The study was performed in a country where withdrawal of life sustaining treatment (WLST) is considered acceptable in patients where the clinical outcome is perceived futile. To conduct a study within a setting whereby WLST is undertaken is important for reliability and applicability. Exclusion and inclusion criteria as well as blinding of the treating clinicians were set appropriately to minimise bias. Given that this was a single-centre study, whereby the WLST was standard, the observed differences in performance between current clinical practice and the additional components analysed as part of the study are not expected to be related to the WLST. However, it should be acknowledged that direct comparison of performance between centres whereby WLST is and is not standard would be more complex. Despite the quantitative nature of the measurements used in this study, the measurement of the SSEP amplitudes remained manual. This might potentially limit the reproducibility of the study methods and findings and lower their overall precision. To minimise the potential effect of bias and variability between the interpreters: a consistent method of definition of baseline and measurement of SSEP amplitude and interpretation of the recording was used, all interpreters had the same experience and skills, they were blinded to each other and a third interpreter was added where differences > 0.1μV noted between the first two interpreters. However, the development and use of an automated and less dependent on interpreters' skills system for quantitative SSEP interpretation would be potentially able to optimise the SSEP interpretation, minimising the variability and the risk of bias and maximise the reproducibility of similar future studies.

The relatively low number of the participants in this study may explain the finding of a clear cut-off point of PTT amplitude size which could achieve 100% NPV and maximum possible PPV for the favourable outcome. It could be expected that changes or variations may exist in the determination of the amplitude of this cut-off point. The potential of amplitude zones of uncertainty above or below this cut-off point cannot be excluded. Larger multi-centre prospective observational studies are needed to define optimally this threshold.

4.5 Key Summary statements

Taking into consideration the above limitations, a summary of the messages which could be drawn are: (i) Peak To Trough amplitude of the 20-30msec complex is more easily measured, achieving 100% inter-interpreter agreement. It has better PPV and specificity than each component of the SSEP alone, without compromising NPV and sensitivity. It is more accurate and reliable at predicting favourable or unfavourable outcome following OHCA and should be a focus for further studies. (ii) The P25/30 as a single measured SSEP demonstrated a higher specificity and higher PPV than N20 (with both qualitative and 0.2 μV threshold analysis). A threshold of 0.5 μV resulted in a misclassification in the prognosis of some patients with favourable outcomes, and so is not clinically recommended. A more optimal threshold may lie somewhere between these two values. (iii) Quantitative interpretation could assist with defining presence or absence of certain SSEP waveforms and could assist with making SSEP interpretation between different centres comparable.

5. CONCLUSION

Enhanced analysis of the 20-30msec somatosensory evoked potential complex could improve accuracy when predicting short-term neurological outcome in comatose survivors of an out of hospital cardiac arrest. Most promising is the amplitude of the Peak to Trough of the 20-30msec complex, measured at 24-36 hours, which has the best sensitivity and specificity for predicting favourable and unfavourable outcomes. Further larger multi-centre studies are needed to optimise amplitude thresholds and reach definitive conclusions.

Sponsor

University Hospitals Plymouth NHS Trust (UHPNT) [RD&I reference: 18/P/088].

Funding

University Hospitals Plymouth NHS Trust Charitable Funds.

Author Contributions

There was an equal contribution from NG and NN and CB for the writing and editing of this manuscript.

CB, NB, LN, LS, ES, AS, NH, NG: members of the study group, contributing to the conduction of the study.

NN, NH, CB, NB, LN: study design.

AB, JC, JH: statistical analysis of the study and editing of the manuscript.

NN, NG, AB, JC, JH: writing of the study report.

Study's references and approvals

RD&I reference: 18/P/088

REC reference: 18/NW/0623

IRAS Number: 251827

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Study Management

The Departments of Intensive Care Medicine [Dr Nikitas Nikitas] and Neurophysiology [Mrs Nicola Broomfield and Mr Nigel Hudson] at Derriford Hospital, University Hospitals Plymouth NHS Trust.

References

Allison T, McCarthy G, Wood C, Jones SJ. Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. A review of scalp and intracranial recordings. *Brain*. 1991;114:2465-503. doi: 10.1093/brain/114.6.2465

Benghanem S, Nguyen LS, Gavaret M, Mira JP, Pène F, Charpentier J, Marchi A, Cariou A. SSEP N20 and P25 amplitudes predict poor and good neurologic outcomes after cardiac arrest. *Ann Intensive Care*. 2022;12(1):25. doi: 10.1186/s13613-022-00999-6.

Carrai R, Scarpino M, Lolli F, Spalletti M, Lanzo G, Peris A, Lazzeri C, Amantini A, Grippo A. Early-SEPs' amplitude reduction is reliable for poor-outcome prediction after cardiac arrest?. *Acta Neurol Scand*. 2019;139(2):158-65.

Endisch C, Storm C, Ploner CJ, Leithner C. Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study. *Neurology.* 2015;85(20):1752-60. doi: 10.1212/WNL.0000000000002123.

Glimmerveen AB, Keijzer HM, Ruijter BJ, Tjepkema-Cloostermans MC, van Putten MJAM, Hofmeijer J. Relevance of Somatosensory Evoked Potential Amplitude After Cardiac Arrest. *Front Neurol*. 2020;11:335. doi: 10.3389/fneur.2020.00335.

Hakimi K, Kinney G, Kraft G, Micklesen P, Robinson L. Reliability in interpretation of median somatosensory evoked potentials in the setting of coma: factors and implications. *Neurocrit Care*. 2009;11(3):353-61. doi: 10.1007/s12028-009-9251-7.

Kim SW, Oh JS, Park J, Jeong HH, Kim JH, Wee JH, Oh SH, Choi SP, Park KN; Cerebral Resuscitation and Outcome evaluation Within catholic Network (CROWN) Investigators. Short-Latency Positive Peak Following N20 Somatosensory Evoked Potential Is Superior to N20 in Predicting Neurologic Outcome After Out-of-Hospital Cardiac Arrest. *Crit Care Med*. 2018;46(6):e545-e551. doi: 10.1097/CCM.0000000000003083. PMID: 29498940.

Oh SH, Park KN, Choi SP, Oh JS, Kim HJ, Youn CS, Kim SH, Chang K, Kim SH. Beyond dichotomy: patterns and amplitudes of SSEPs and neurological outcomes after cardiac arrest. *Crit Care*. 2019;23(1):224. doi: 10.1186/s13054-019-2510-x.

Pfeifer R, Weitzel S, Günther A, Berrouschot J, Fischer M, Isenmann S, Figulla HR. Investigation of the inter-observer variability effect on the prognostic value of somatosensory evoked potentials of the median nerve (SSEP) in cardiac arrest survivors using an SSEP classification. *Resuscitation*. 2013;84(10):1375-81. doi: 10.1016/j.resuscitation.2013.05.016.

Resuscitation Council (UK): Post resuscitation Care Guidelines. Resuscitation Council 2021.

Sandroni C, Cavallaro F, Callaway CW, Sanna T, D'Arrigo S, Kuiper M, Della Marca G, Nolan JP. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 1: patients not treated with therapeutic hypothermia. *Resuscitation*. 2013;84(10):1310-23. doi: 10.1016/j.resuscitation.2013.05.013.

Sekhon MS, Ainslie, PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a “two-hit” model. *Crit Care*. 2017;21:90.

van Soest TM, van Rootselaar AF, Admiraal MM, Potters WV, Koelman JHMT, Horn J. SSEP amplitudes add information for prognostication in postanoxic coma. *Resuscitation.* 2021;163:172-175. doi: 10.1016/j.resuscitation.2021.03.033.

Witten L, Gardner R, Holmberg MJ, Wiberg S, Moskowitz A, Mehta S, Grossestreuer AV, Yankama T, Donnino MW, Berg KM. Reasons for death in patients successfully resuscitated from out-of-hospital and in-hospital cardiac arrest. *Resuscitation*. 2019;136:93-99.

Zandbergen EG, Koelman JH, de Haan RJ, Hijdra A; PROPAC-Study Group. SSEPs and prognosis in postanoxic coma: only short or also long latency responses? *Neurology.* 2006;67(4):583-6. doi: 10.1212/01.wnl.0000230162.35249.7f.

Figure Legends

Figure 1

a) The challenge with current somatosensory evoked potential (SSEP) analysis whereby, after resuscitation and admission post cardiac arrest, during neuro-prognostication, the presence of the N20 SSEP lacks the strong predictive certainty for a favourable outcome as seen with the absent N20 SSEP and the unfavourable outcome, b) Left: schematic representation of an SSEP waveform with the positive deflection being the N20, and the following negative deflection the P25/30. Right: By measuring the amplitude between the N20 and P25/30, the peak-to-trough amplitude can be interpreted, C) Determination of whether a waveform is truly present could be complicated by unstable baseline or background noise.

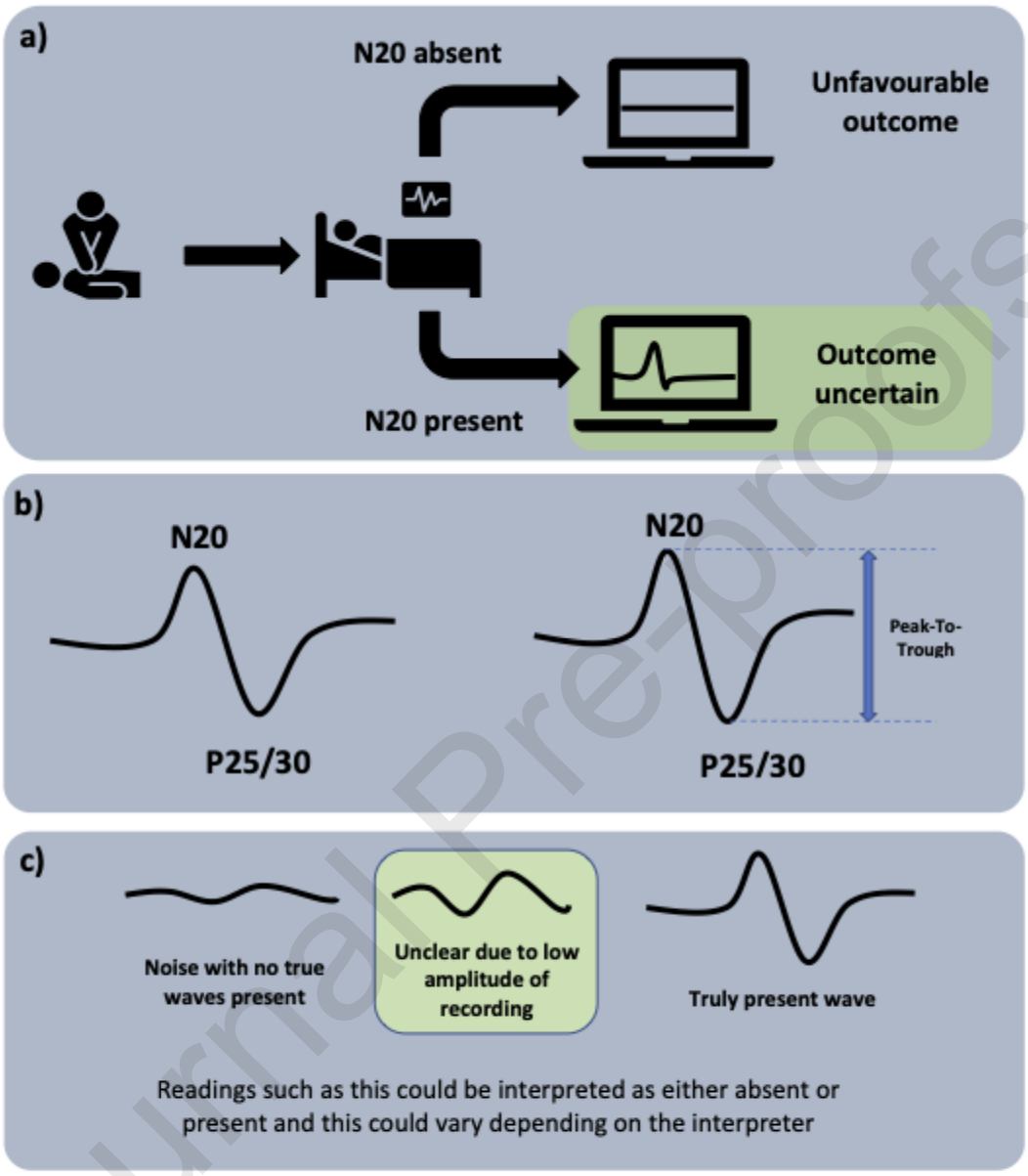


Figure 2

Study protocol of somatosensory evoked potential recording.

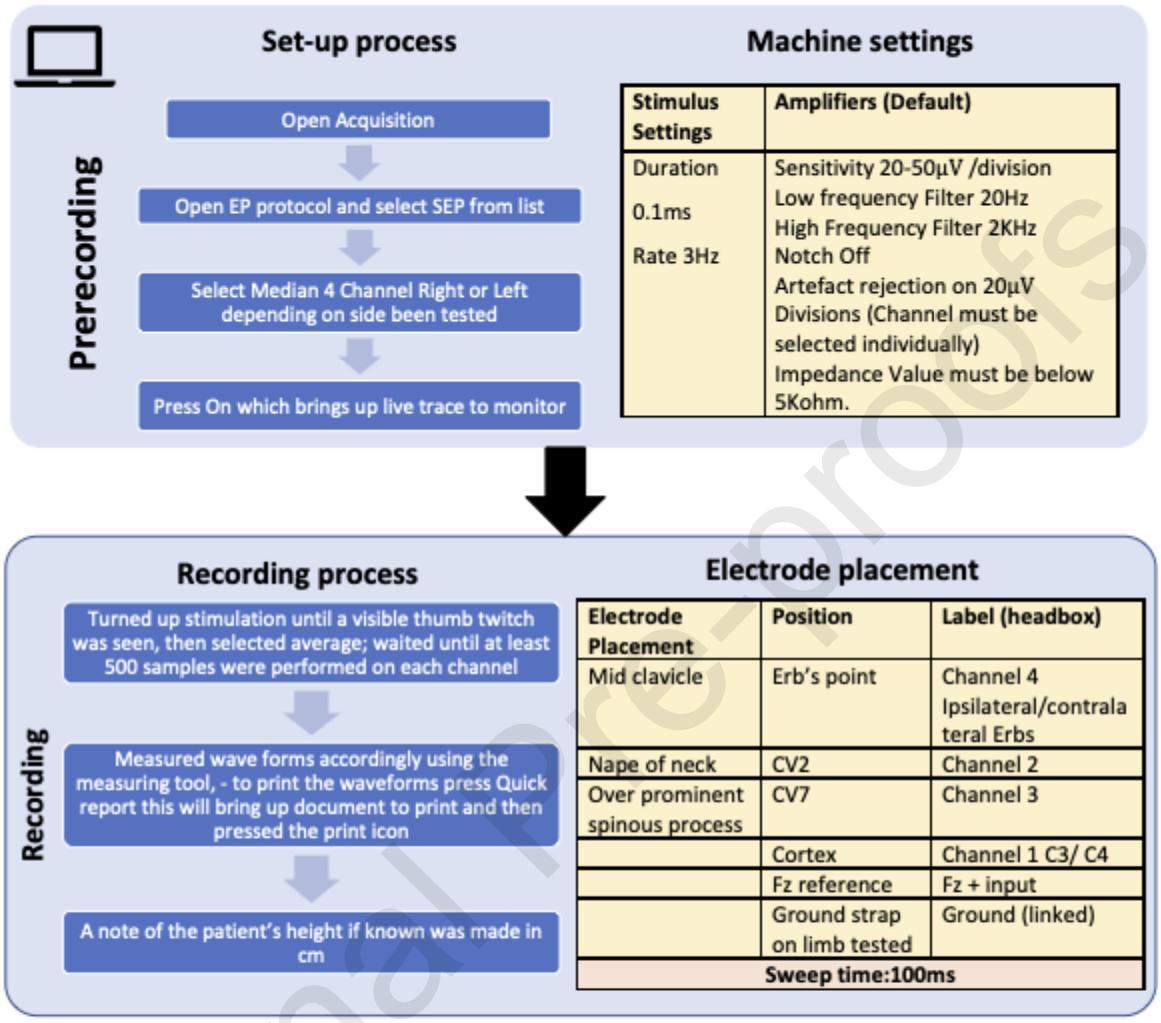


Figure 3

Somatosensory evoked potential interpretation process post recording. For each recording, the same steps of interpretation were taken by the interpreters. An initial qualitative analysis for the presence/absence of the N20, then utilising threshold analysis at both 0.5 μV and 0.2 μV, the P25/30 and N20 peaks were recorded as either absent or present depending on whether their amplitude from baseline met this threshold. Finally peak-to-trough was measured, and its prognostic value was tested against the threshold of 0.6 μV.

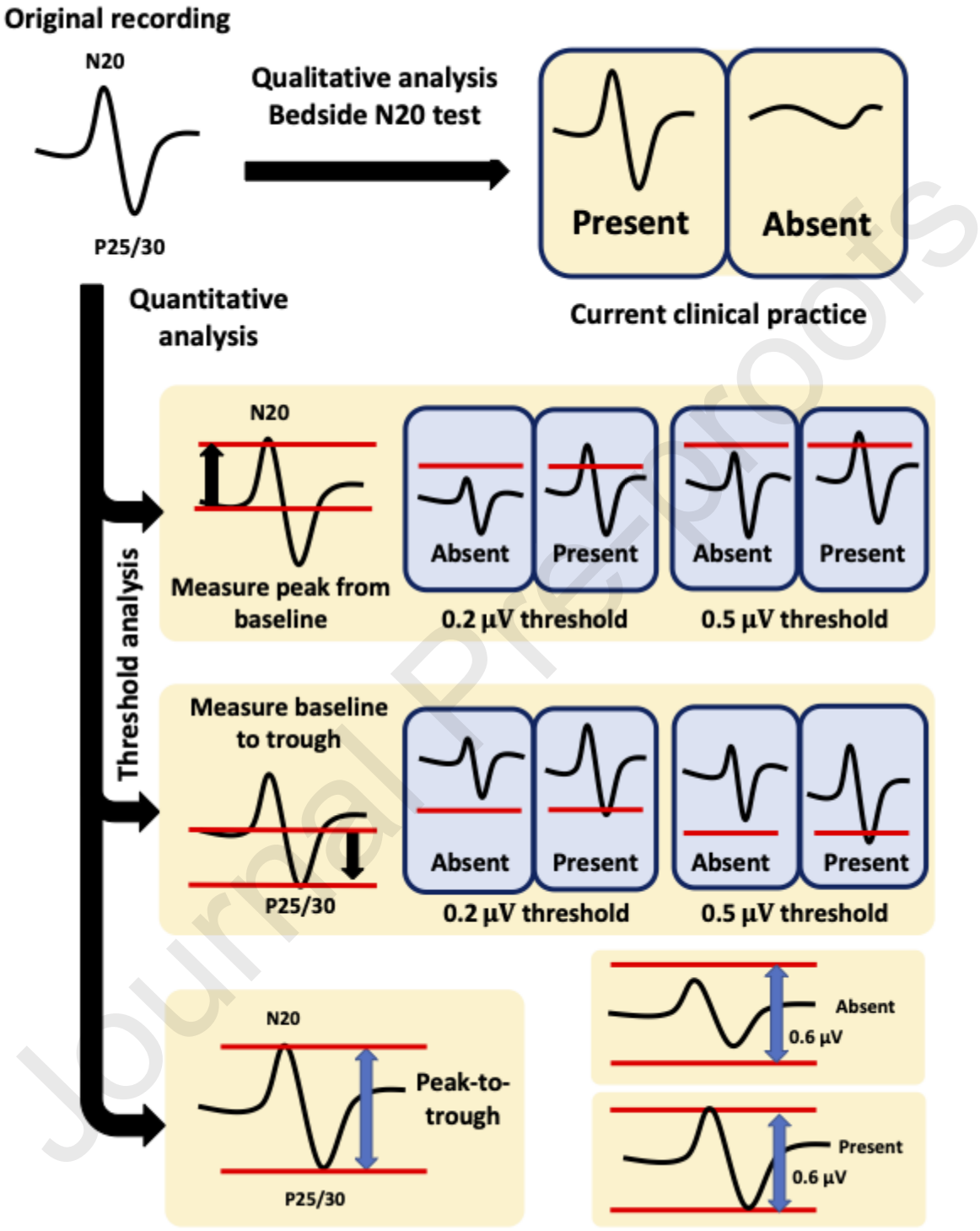


Figure 4

Examples of original study somatosensory evoked potential (SSEP) recordings as seen by interpreters and the amplitude measurements for P25/30, N20 and peak-to-trough. For the N20 SSEP, an example of recordings which meet the 0.5 μV, the 0.2 μV threshold and not meeting either is shown. μV: microvolts.

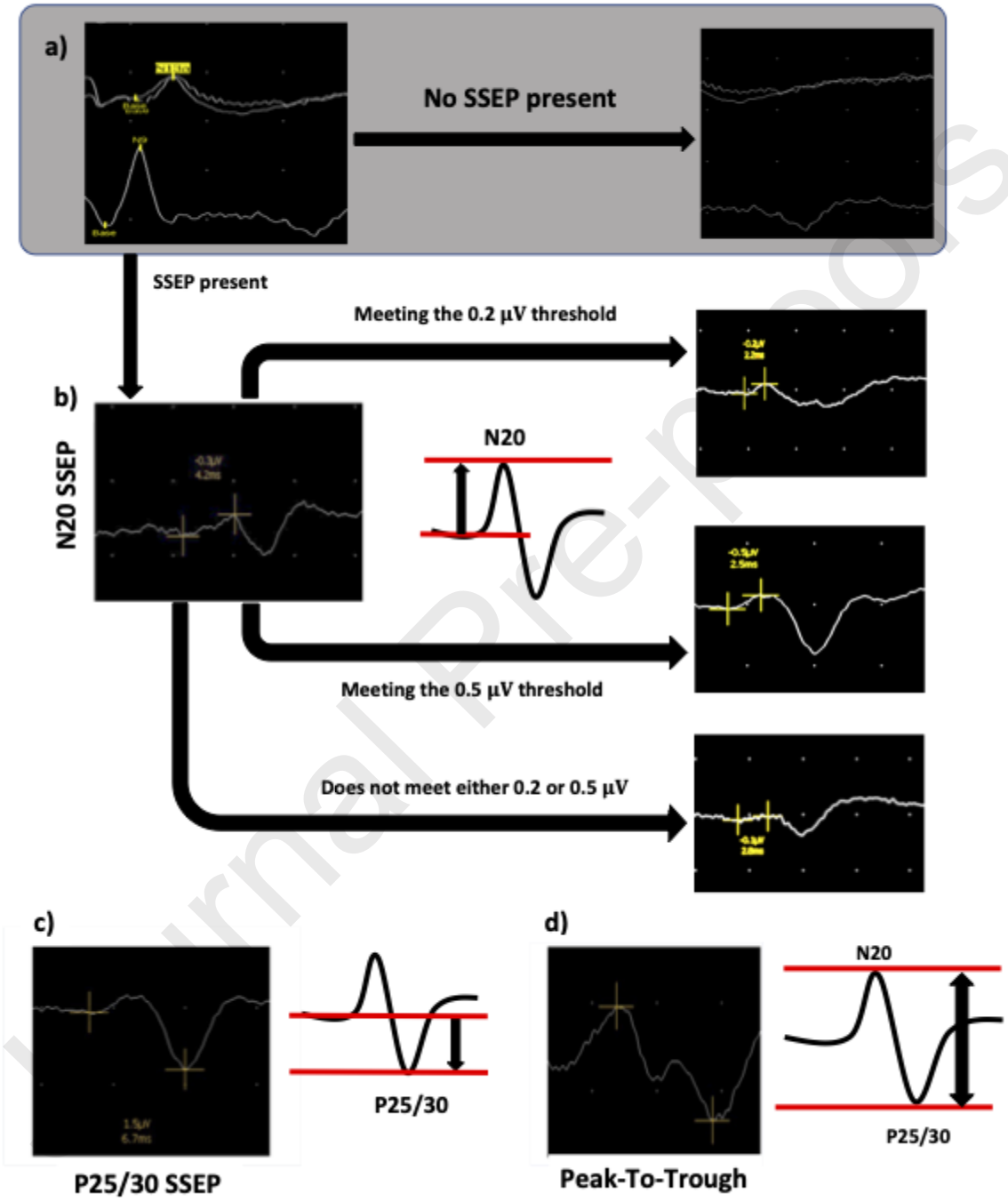


Figure 5

Flow diagram of the study showing number of patients screened, enrolled, and analysed. [*1: Inability to obtain a recording due to severe-previously undiagnosed diabetic peripheral neuropathy with absence of conduction of sensory stimulus even at the maximum frequency and intensity of stimulation. Absence of N9-N13 somatosensory evoked potentials. 2: Identified later that somatosensory evoked potential (SSEP) recording was done at temperature < 36 degrees Celsius]. ** Participant number 26: The participant died from multiple organ failure without escalation to further organ support due to patient's previous wishes and previous comorbidities. The sedation remained off for 12 hours before commencement of end-of-life treatment but during this period patient was on multiple organ failure with high lactate. Therefore, the study team after reviewing the case, decided that the assessment of cerebral performance category (CPC) was not reliable under these conditions. The death could not be attributed directly to hypoxic brain injury as the neurological outcome could not be assessed given that the patient never recovered from multiple organ failure and withdrawn < 72 hours after intensive care unit (ICU) admission. The reason for withdrawal was not low Glasgow Coma Scale (GCS) but irreversible multiple organ failure Participant number 63: The participant died from multiple organ failure, the sedation remained off for appropriate period of time, but the CPC could not reliably be assessed as it was constantly fluctuating due to respiratory and cardiac failure with hypoxia and hypercapnia and respiratory distress. The outcome was not related to brain injury so CPC cannot be reliably assessed. Participant number 44: The participant died on sedation due to myoclonic jerks [Not myoclonic status, as this had been ruled out by electroencephalogram (EEG) recording]. Unable to assess CPC. Participant number 87: The participant died on propofol. Unable to assess CPC.

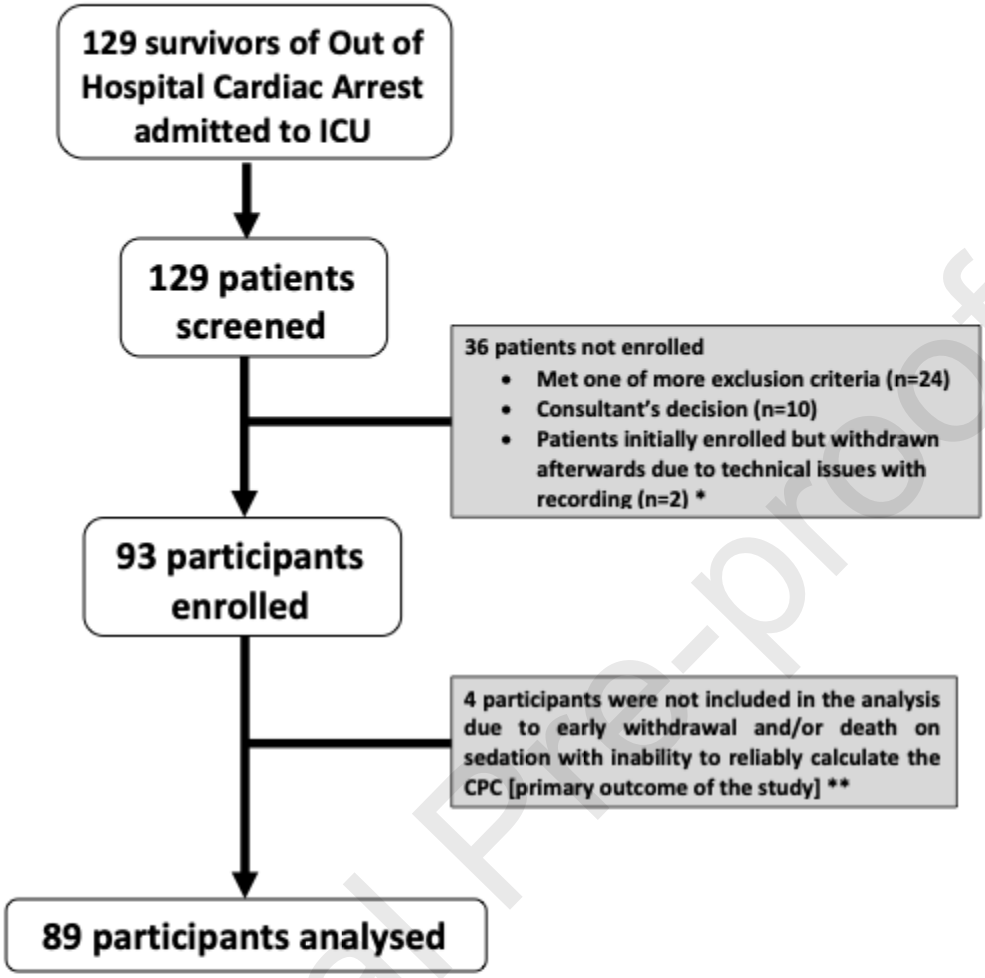


Figure 6

Graph of positive predictive values for comparative performance of the different analytical approaches of somatosensory evoked potentials.

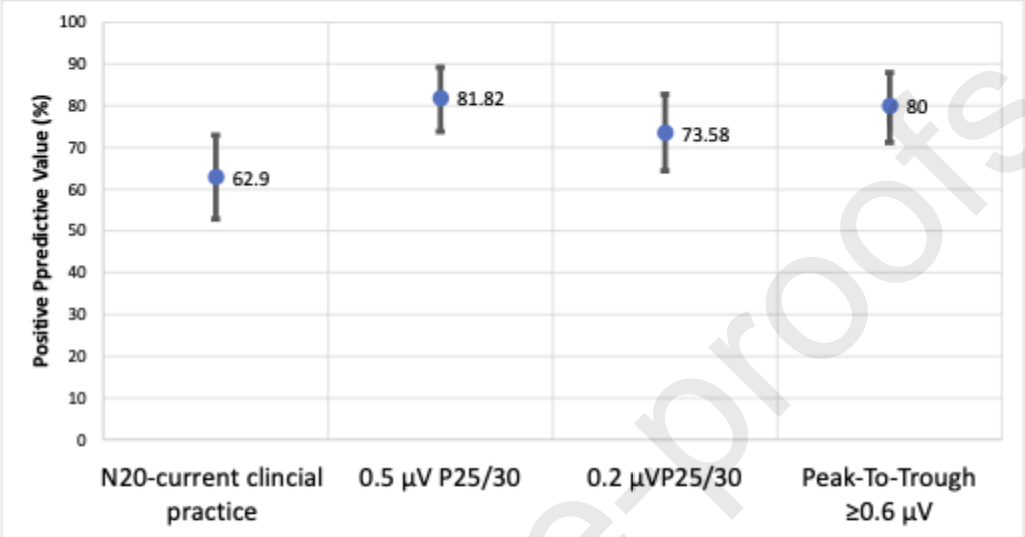
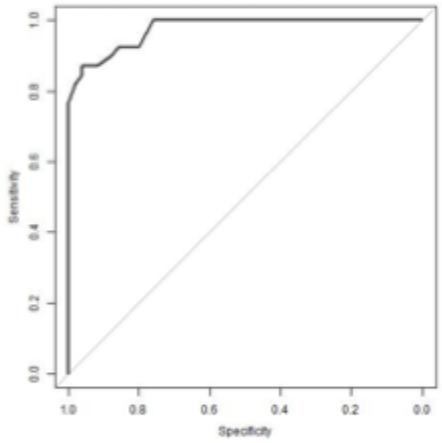
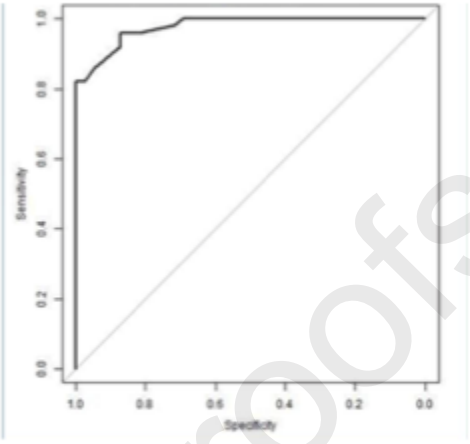
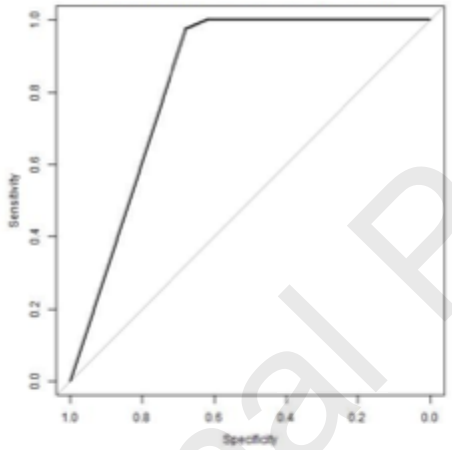


Figure 7

Receiver operator characteristic curves of performance- top left: N20 somatosensory evoked potential (SSEP) [using 0.2 μV threshold to define its presence] Top right P25/30 SSEP [using 0.2 μV threshold to define its presence] and bottom left: Peak To Trough amplitude of the 20-30msec complex [using the cut – off level of 0.6 μV for correlation with outcome].







Inclusion criteria	Exclusion criteria
All adult comatose survivors after out of hospital cardiac arrest who are admitted to Derriford Hospital Intensive Care Unit. The cause of cardiac arrest may be cardiac and/or non-cardiac or unknown at the time of enrolment.	Non-comatose patients after return of spontaneous circulation (ROSC)
All patients must be comatose before intubation [Glasgow coma scale (GCS) equal or lower than 8].	Coma secondary to Intracranial and Intracerebral haemorrhage
All patients must be on one or more invasive organ support [e.g. Endotracheal intubation and mechanical ventilation, vasopressor and/or inotropic support, Continuous Renal Replacement Therapy Sedated and/or on neuromuscular blocking agents].	Patients with haemorrhagic shock
All patients must be sedated before and during the time of somatosensory evoked potential (SSEP) recording. If clinically indicated, neuromuscular blocking agents may also be used.	Patients with severe neurologic disability [cerebral performance category (CPC) level higher than 2] during the pre-cardiac arrest period
All patients must be on targeted temperature management as per Derriford intensive care unit (ICU) policy and protocol: For the first 24 hours after ICU admission, the target-temperature is 36°C with temperature control commencing within the first hour after critical care admission. For the next 48 hours the temperature of the patients will be maintained between 36-37°C. The temperature targets are achieved with external cooling devices.	Presence of active Demyelinating disease or past medical history of Demyelinating disease
Patients must have a computed tomography (CT) scan of the head if severe cerebral pathology which is part of the exclusion criteria is clinically suspected.	Trauma-induced Cardiac arrest
Absence of all exclusion criteria	Previously or during the current admission diagnosed Spinal Cord and /or brain stem lesions

	Patients with Implantable defibrillator device [incompatibility with SSEP recordings device]

Table 1: Inclusion and exclusion criteria.

Neurological outcome	CPC	
Favourable	1	Full recovery or mild disability
	2	Moderate disability but independent in activities of daily living (ADLs)
Unfavourable	3	Severe disability-Dependent in ADLs
	4	Persistent vegetive state
	5	Death

Table 2: CPC (cerebral performance category) score

	% of all enrolled participants (number of participants)		P Value
	Favourable	**Unfavourable**	
Number of participants	43.8% (39)	56.2 (50)	

Mortality (at discharge or 28 days)	2.6 (1)	98% (49)	
Sex **Male** **Female**	 43.9 (29) 43.5 (10)	 56.1 (37) 56.5 (13)	>0.1
Comorbidities **Yes** **No**	 25.8 (23) 18.0 (16)	 36.0 (32) 20.2 (18)	>0.1
Cardiac arrest cause **Cardiac** **Non-cardiac** **Unknown**	 38.2 (34) 5.6 (5) 0.0 (0)	 34.8 (31) 20.2 (18) 1.1 (1)	<0.05
Cardiac arrest rhythm **Asystole** **PEA** **VF** **pVT**	 0.0 (0) 5.6 (5) 38.2 (34) 0.0 (0)	 7.9 (7) 23.6 (21) 23.6 (21) 1.1 (1)	<0.001
Bystander CPR **Yes** **No**	 39.3 (35) 4.5 (4)	 46.1 (41) 10.1 (9)	>0.1
CT head scan **Yes-Normal**	 29.2 (26)	 23.6 (21)	<0.01

Yes-Abnormal **Not done**	4.5 (4) 10.1 (9)			23.6 (21) 9.0 (8)		
	Mean	**Median**	**SD**	**Mean**	**Median**	**SD**
Age (years)	58.4	58.0	14.0	58.9	58.0	14.8
Anoxic time (mins)	21.0	16.0	12.8	36.2	27.5	34.3
Length of ICU stay (days)	7.1	5.0	5.2	6.5	4.0	8.8

Table 3: Demographic and clinical data as well as CPC score of the study participants in the two neurological outcome groups. SD, standard deviation; PEA, pulseless electrical activity; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia; CPR, cardiopulmonary resuscitation; CT, computed tomography

For the prediction of the present SSEP and favourable outcome	**Prognostic values of P25/30 and PTT compared to current clinical practice (numbers represent %)**			
	N20-current clinical practice	**P25/30 threshold**		**PTT (use of cut-off amplitude of ≥0.6μV)**
		0.5μV	**0.2μV**	
PPV	62.90	81.82	73.58	80.00
NPV	100	93.33	100	100
Specificity	54.0	84.0	72.00	80.00
Sensitivity	100	92.31	100	100

FPR	46.0	16.0	30.00	20.00

Table 4: Results of the final analysis showing the comparative performance of the P25/30 and PTT against the current clinical practice with respect to positive predictive value (PPV), negative predictive value (NPV), specificity, sensitivity, and false positive rate (FPR). These are all with respect to the presence of the somatosensory evoked potential (SSEP) and a favourable outcome. It is shown that compared to current clinical practice, the use P25/30 and PTT improved these performance measures. μV: microvolts