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Short paper

SSEP amplitudes add information for prognostication in postanoxic coma

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Abstract

Objective: To investigate whether somatosensory evoked potential (SSEP) amplitude adds information for prediction of poor outcome in postanoxic coma.

Methods: In this retrospective cohort study we included adult patients admitted after cardiac arrest between January 2010 and June 2018 who remained in coma and had SSEP recorded for prognostication. Outcome was dichotomized in poor (Cerebral Performance Category (CPC) 4–5) and good (CPC 1–3) at ICU discharge. Sensitivity of bilaterally absent N20 potential was calculated. In case the N20 potential was not bilaterally absent, the amplitude contralateral to stimulation side (baseline-N20, N20-P25, and maximum) was determined. At a specificity of 100%, SEPP amplitude sensitivities were determined for poor outcome.

Results: SSEP recordings were performed in 197 patients of whom 57 had bilaterally absent N20 potentials. From 140 patients, 16 (11%) had a good outcome. The sensitivity for poor outcome of bilaterally absent N20 was 31%. At a specificity of 100%, contralateral amplitude thresholds were 0.34 μV (baseline-N20), 0.99 μV (N20-P25) and 1.0 μV (maximum), corresponding to a sensitivity for poor outcome of 38%, 44% and 40%. Combination of bilaterally absent N20 and a N20-P25 threshold below 0.99 μV yielded a sensitivity of 62%.

Conclusions: Our results confirm that very low cortical SSEP amplitudes are highly predictive of poor outcome in patients with postanoxic coma. Adding 'N20-P25 threshold amplitude' to the 'bilaterally absent N20' criterion, increased sensitivity substantially.

Keywords: Cardiac arrest, Somatosensory evoked potentials, Amplitude, Prognostication, Outcome

Introduction

Bilateral absence of contralateral cortical responses (N20) in median nerve somatosensory evoked potentials (SSEP) reliably predicts poor outcome in patients who remain in coma after cardiac arrest and is part of the international guidelines.[1,2] However, interpretation of the recordings can be difficult and sensitivity is low.[3] Amplitude assessment of the cortical responses might be a useful addition, with very low amplitudes predicting a poor outcome. Research on this topic is limited but results so far are comparable.[4–8] We aimed to investigate whether somatosensory evoked potential (SSEP) amplitude adds information for prediction of poor outcome in postanoxic coma.

Methods

We retrospectively studied all adult patients with postanoxic coma after cardiac arrest in whom a median nerve SSEP was recorded for prognostication in the Amsterdam UMC, location AMC, from January 2010 to June 2018. SSEPs were recorded after targeted temperature

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management (TTM) for 24 h and clearance of sedative medication. The need for informed consent was waived by the Medical Ethical Committee of the Amsterdam UMC, location AMC. Baseline characteristics of the patients were collected from the medical file.

SSEP recording

SSEPs were recorded using clinical Natus equipment (Natus Medical Inc, CA, USA) with silver chloride skin electrodes placed bilaterally at Erb's point, spinous process of C5 (neck), and on the skull on CP3/C3′, CP4/C4′, Fz (reference for CP3/C3′ and CP4/C4′) and Cz (reference for Erb's point and the spinous process electrode). Either CP3 and CP4 or C3′ and C4′ were used, depending on date of recording. Two series of 512 stimuli, at a rate of 4 Hz, were recorded resulting in two waveforms of the averaged stimuli. To minimize muscle artifacts, neuromuscular blocking medication was administered if necessary.

SSEP evaluation

All SSEP recordings were assessed in the clinical setting by trained clinical neurophysiologists who scored, based on criteria of Zandbergen et al., whether the N20 was 'bilaterally absent'.[3] When peripheral responses at Erb's point or cervical level were absent, the recording was excluded from the current analysis. When N20 was not judged as 'bilaterally absent', three methods for amplitude measurement were used in both waveforms (two series of stimuli) of: (1) baseline-N20; (2) N20-P25; and (3) maximum peak amplitude between 4.5 and 50 milliseconds (ms) after stimulation. In this last method, the highest of either baseline-N20, N20-P25 or P25-N35 was used (see Fig. 1). Markers for amplitude calculation were placed offline, while blinded for patient's outcome. When in doubt, the location of the marker was discussed with an experienced clinical neurophysiologist (AFvR). For analysis, the highest amplitude measures per waveform per peak (method 1–3) were used. Noise levels were estimated taking both the slow (±100 Hz) and fast waves (±1000 Hz) into account. When the maximum noise level was >0.25 μV with maximum amplitudes <1.0 μV, the recording was excluded.

Other prognostication methods and outcome

Data on pupillary reflexes, electroencephalography (EEG) and neurological outcome at Intensive Care Unit discharge was retrieved from the medical files and categorized as poor or good according to the Glasgow-Pittsburgh Cerebral Performance Categories (CPC).[9] We considered CPC 4–5 (vegetative state or (brain)death) as poor outcome and CPC 1–3 (no, minimal, moderate or severe neurological deficit) as good outcome.

Analysis

For the three methods of amplitude measurement, the threshold was determined by using the lowest amplitude in the group with good outcome. This yielded in a specificity of 100%. With these thresholds, sensitivity for poor outcome prediction was calculated. Combined sensitivity of bilaterally absent N20 and low amplitude threshold was calculated.

Results

For this study, 225 patients initially fulfilled the inclusion criteria. Registrations with absent peripheral responses (5) and high noise levels (23) were excluded. Of the remaining 197 patients, 181 (92%) had a poor outcome. From these 181 patients, 57 had a bilaterally absent N20, leading to a sensitivity of 31% (95% CI 25–39). Amplitudes were determined in SSEP registrations of 140 patients (197–57), of whom 24% were female. The mean age of these patients was 64 years (standard deviation (SD) 15). There were no differences between patients with a good or a poor outcome for these characteristics.

SSEP amplitude thresholds

No patient with a good outcome had a baseline-N20 amplitude below 0.34 μV, a N20-P25 amplitude below 0.99 μV or a maximum amplitude below 1.00 μV. Amplitude distributions are shown in Fig. 2. Using the N20-P25 amplitude threshold, 55 of the 124 patients

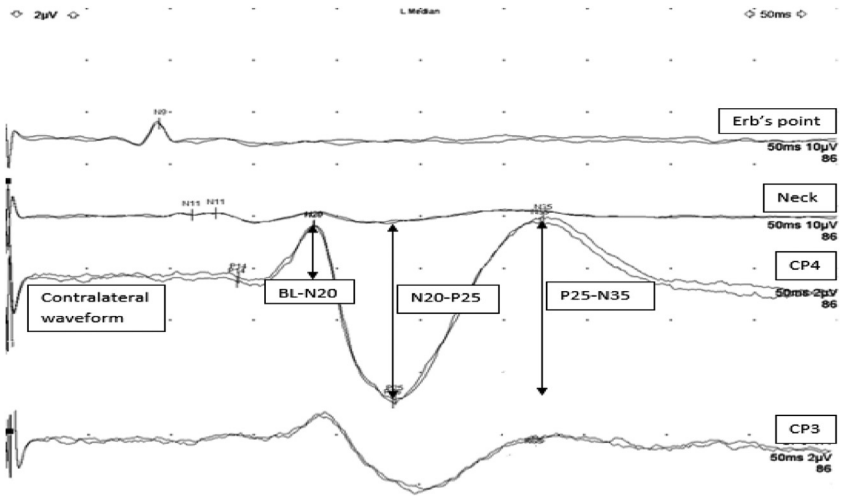

Fig. 1 – Representative left median SSEP result in a patient in our cohort. Two sets of 512 responses at a rate of 4 Hz, were averaged. Recorded by electrodes at 2 cm or 1 cm posterior to C3 and C4 (C3′/C4′). Fz was used as reference.

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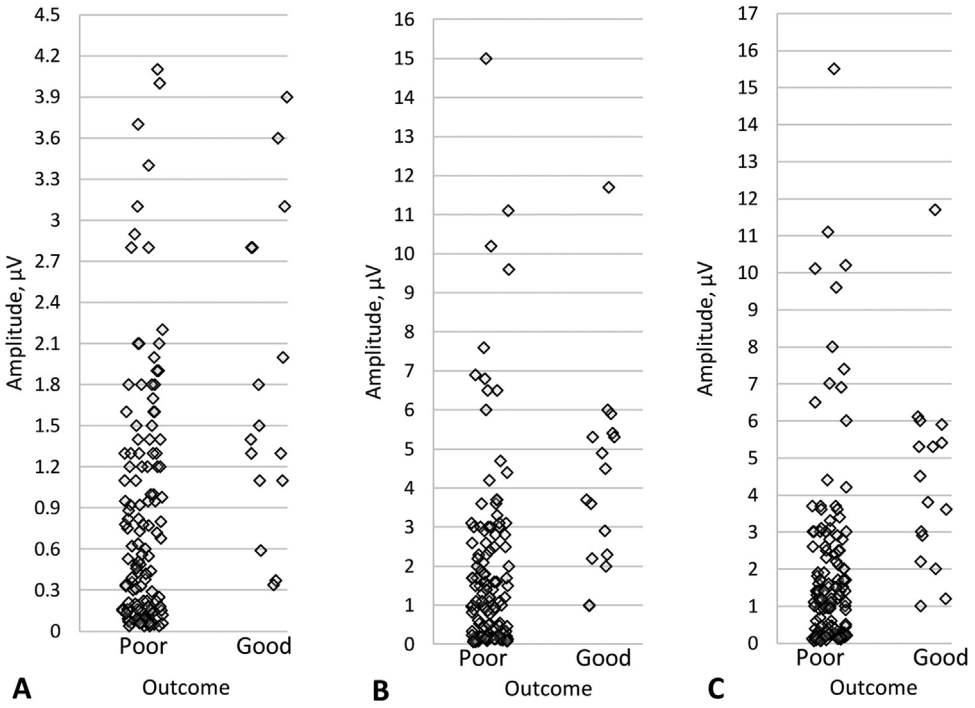

Fig. 2 – Scatterplots for the baseline-N20 amplitude (A), N20-P25 amplitude (B) and maximum amplitude from 4.5 to 50 ms (C). Amplitude on the y-axis and outcome on the *x*-axis.

with a poor outcome and no bilaterally absent N20 would have been detected, yielding a sensitivity of 44% (Table 1). When combining this data with patients with a bilaterally absent N20, a sensitivity of 62% was found. Data on pupillary reflexes was available from 48 of the 55 patients with a N20-P25 amplitude below 0.99 μV, excluding patients with a bilaterally absent N20, of whom 7 had absent pupillary reflexes (15%). An EEG was recorded in 43 of these 55 patients (after the SSEP), of whom 12 (28%) had a low voltage EEG (<20 μV), 6 (14%) had a burst-suppression pattern and 11 (26%) had a status epilepticus.

Discussion

Our study confirms that very low SSEP amplitudes are strongly associated with poor outcome in patients with postanoxic coma and therefore have the potential to become a prognostic marker to be applied in clinical practice. In our cohort, of the three assessment methods, N20-P25 amplitude assessment method was, at a threshold of 0.99 μV, the most sensitive for poor outcome. Combining results of registrations with bilaterally absent N20 and very low SSEP amplitude increased sensitivity substantially.

Our results corroborate the sensitivity of 58% found by Glimmerveen et al., although they found a lower threshold amplitude of 0.4 μV in a study comparable to ours.[8] Similar results were found by Endisch et al. (sensitivity of 57%, threshold of 0.62 μV for the maximum SSEP amplitude from 4.5 to 50 ms).[4] Carrai et al. found an amplitude threshold of 0.65 μV with similar methods.[5] A major difference between our study and the studies by Endisch and Carrai is the population in whom SSEPs were recorded. We recorded SSEPs in patients who remained unconscious after clearance of sedative medication administered in the first 24 h of admission. This leads to a population with a high percentage of poor outcome. The previous studies recorded SSEPs during or shortly after the first 24 h after cardiac arrest, when patients were still sedated. In such a population, more patients wake up and have a good outcome.

Instead of focusing on one amplitude determination method, we compared three methods. The maximum amplitude was previously studied by Endisch et al. and Carrai et al. and was reported to be a reliable predictor of poor outcome.[4,5] In 2003, a small study by Logi

Table 1 – Results of N20 amplitude assessment and prediction of poor outcome.

Method of amplitude assessment	Threshold (μV)	Patients detected (n/N)	Sensitivity (95% CI)	Combined sensitivity (95% CI)
Baseline-N20 amplitude	0.34	47/124	38% (29–47)	57% (50–65)
N20-P25 amplitude	0.99	55/124	44% (35–54)	62% (54–69)
Maximum amplitude from 4.5 to 50 ms	1.00	49/124	40% (31–49)	59% (51–66)

Table showing threshold amplitudes, number of detected patients with poor outcome and no bilaterally absent N20, sensitivities and combined sensitivities. μV: mircrovolts; ms: milliseconds; CI: confidence interval.

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et al. also showed that low baseline-N20 and N20-P25 are correlated with poor outcome.[6] Similar results were recently reported by Oh et al. and by Barbella et al.[7,10] However, Barbella et al. showed no improvement in univariate prediction by low SSEP amplitude compared to bilateral absence of the N20. Only a very small improvement in sensitivity was found in a multimodal approach using an amplitude threshold of 0.41 μV instead of absence of the N20. Also, 5 patients in their cohort regained consciousness after initially having amplitudes of <0.65 μV. These differences are hard to explain. In a systematic review by Amorim et al., the reliability of absent cortical SSEP responses was recently doubted.[11] These results indicate that correct interpretation of SSEP results is crucial, as medication, body temperature and noise seem to affect the reliability of the registration. These findings underline the importance of a multimodel approach for prognostication.[12]

Recently, Endisch et al. investigated the relation between SSEP amplitudes and histopathologically determined severity of postanoxic encephalopathy.[13] They found that no patient with no or mild postanoxic encephalopathy had SSEP amplitudes < 0.5 μV. This shows that very low SSEP amplitudes also strongly predict severe brain damage and therefore supports our results.

The results of our study do not suffer from self-fulfilling prophecy as all patients with bilateral absence of N20, in whom life sustaining therapy was stopped, were excluded from amplitude analysis. No decisions were based on the N20 amplitude or other cortical waveform amplitudes.

A limitation of our study is the limited number of patients with a good outcome. This potentially influences the amplitude threshold that we found. Furthermore, sedation and body temperature were not considered in detail, although sedation was stopped and recordings were made after TTM. These factors have been shown to not affect N20 amplitude significantly.[4,5] Nevertheless, the threshold values are relatively high compared to previous studies and should be interpreted with caution.

In conclusion, very low cortical SSEP amplitudes are predictive of poor outcome in patients after cardiac arrest. Combining bilaterally absent N20 and very low SSEP amplitude increases sensitivity substantially.

Conflict of interest

None.

Authors' contribution

Thijs M. van Soest: Methodology, Formal analysis, Investigation, Writing – original draft, Visualization; **Anne-Fleur van Rootselaar**: Methodology, Writing – review and editing, Supervision; **Marjolein M. Admiraal**: Investigation, Writing – review and editing; **Wouter V. Potters**: Software, Writing – review and editing; **Johannes H.M.T. Koelman**: Writing – review and editing; **Janneke Horn**: Methodology, Writing – review and editing, Supervision.

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