Somatosensory evoked potentials during mild hypothermia after cardiopulmonary resuscitation

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ABSTRACT

Objective: In patients who remain in a coma after cardiopulmonary resuscitation (CPR), the bilateral absence of cortical N20 responses of median nerve somatosensory evoked potentials (SSEP) 24 hours after admission invariably correlates with a poor neurologic outcome. Nowadays, CPR patients are treated with mild hypothermia, with simultaneously administered sedative drugs, hampering clinical neurologic assessment. We investigated whether SSEP performed during hypothermia can reliably predict a poor neurologic outcome.

Methods: Between July 2006 and April 2008, this multicenter prospective cohort study included adult comatose patients admitted after CPR and treated with induced mild hypothermia (32–34°C). SSEP was performed during hypothermia, and in patients who remained comatose after rewarming, a second SSEP was performed. Neurologic outcome was assessed 30 days after admission with the Glasgow Outcome Scale.

Results: Seventy-seven consecutive patients were included in 2 hospitals. In 13 patients (17%), the cortical N20 response during hypothermia was bilaterally absent. In 9 of these 13 patients in whom SSEP could be repeated during normothermia, the N20 response was also absent, yielding a positive predictive value of 1.00 (95% confidence interval [CI] 0.70–1.00). All 13 patients with absent SSEP during hypothermia had a poor neurologic outcome, yielding a positive predictive value of 1.00 (95% CI 0.77–1.00).

Conclusions: The results of this pilot study show that bilaterally absent cortical N20 responses of median nerve somatosensory evoked potentials performed during mild hypothermia after resuscitation can predict a poor neurologic outcome. We started a larger multicenter prospective cohort study to confirm these results. ***Neurology*® 2009;73:1457–1461**

GLOSSARY

CI = confidence interval; **CPR** = cardiopulmonary resuscitation; **GOS** = Glasgow Outcome Scale; **SSEP** = somatosensory evoked potentials.

Prediction of neurologic outcome in comatose survivors of cardiopulmonary resuscitation (CPR) has been the subject of several studies in the last 2 decades. In comatose survivors of CPR, the bilateral absence of cortical N20 responses of the median nerve somatosensory evoked potentials (SSEP) was invariably correlated with a poor neurologic outcome.[1,2] In 2002, 2 randomized controlled trials showed that induced mild hypothermia (32–34°C) decreases mortality and improves neurologic outcome in adult comatose survivors of out-of-hospital cardiac arrest with ventricular fibrillation as initial rhythm.[3,4] Soon thereafter, this treatment was incorporated in guidelines of the International Liaison Committee on Resuscitation and the American Heart Association.[5,6] The administration of sedative drugs during hypothermia hampers neurologic assessment and delays prediction of neurologic outcome, leading to uncertainty in family members and treating physicians and potentially unnecessary prolongation of intensive care unit treatment. The effect of reduced temperature on SSEP responses in these

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patients is uncertain and therefore it is unknown whether this tool can be used for prognostication in this situation. The aim of this study was to investigate whether median nerve SSEP during mild hypothermia can be used to predict neurologic outcome in comatose patients after CPR.

METHODS In this prospective cohort study in 2 centers, 1 academic and 1 teaching hospital, we included patients between July 2006 and April 2008. Comatose patients, admitted to the intensive care unit after CPR and treated with induced mild hypothermia (32–34°C), were included. Exclusion criteria were age <18 years, confirmed brain death before treatment, concomitant traumatic brain injury, discontinuation of hypothermia due to complications, impossibility to perform SSEP (during weekends), and absence of informed consent.

Standard protocol approvals, registrations, and patient consents. The protocol and consent procedures were approved by the ethics committees of the 2 collaborating hospitals. Informed consent was obtained from a legal representative shortly after admission. When the patient regained consciousness and was able to judge his or her situation properly, informed consent was also obtained from the patient.

The hypothesis of the study was that patients with a bilaterally absent cortical N20 response of median nerve SSEP during mild hypothermia also had absent cortical N20 responses after regaining normothermia. A secondary hypothesis was that an absent SSEP during treatment with mild hypothermia is always correlated with a poor neurologic outcome.

Primary endpoint was the result of SSEP performed during normothermia. Secondary endpoint was neurologic outcome assessed with the Glasgow Outcome Scale (GOS), 30 days after admission by telephone interview with the patient or his or her legal representative.[7] The interviewer was not aware of the SSEP results. Poor outcome was defined as death or vegetative state (GOS 1–2).

Somatosensory evoked potentials. The left and right median nerve were stimulated at the wrist with a bipolar surface electrode with a repetition rate of 2 to 5 Hz and a stimulus duration of 0.2 msec. Filter bandpass was 3 Hz–2 kHz or 20 Hz–2 kHz. Two sets of 512 responses were averaged. Surface electrodes were placed at Erb's point, cervical spine, and 3.0 cm posterior to C3 and C4 according to the International 10–20 system. The results for the cortical N20 response were documented as absent, present, or technically undeterminable. The median nerve SSEP was defined as absent if the cortical N20 response was absent on both sides after left and right sided median nerve stimulation, in the presence of a cervical potential. The SSEP was defined as present if the cortical N20 response was present at one or both sides. The results of hypothermic SSEP were not available for treating physicians in order to avoid any influence on treatment decisions of the test results. In patients who remained in a coma after regaining normal body temperature and wearing off of sedative drugs, a second SSEP was performed. The results of these normothermic SSEP were disclosed to the treating physicians. In case of absent cortical responses in the normothermic SSEP, supportive treatment was withdrawn, leading to death in hours to days. Additional data collected were gender, age, resuscitation characteristics, neurologic examination, and use of sedative drugs.

Table 1 Baseline characteristics and neurologic outcome

Characteristics	Values
Age, y, median (IQR)	65 (50–77)
Gender, % (n)	
Male	71 (55)
Female	29 (22)
Time from collapse to start resuscitation, % (n)	
No delay	41.6 (32)
1–5 min	24.7 (19)
6–10 min	15.6 (12)
11–20 min	2.6 (2)
Unknown	15.6 (12)
Resuscitation duration, min, median (IQR)	15 (10–35)
GOS after 30 days, % (n)	
1 Death	66.2 (51)
2 Vegetative state	0 (0)
3 Severe disability	6.5 (5)
4 Moderate disability	6.5 (5)
5 Good recovery	20.8 (16)
Resuscitation cause, % (n)	
Cardiac arrest	89.6 (69)
Hypoxemia	9.1 (7)
Unknown	1.3 (1)
Initial rhythm, % (n)	
Ventricular fibrillation	66.2 (51)
Asystole	19.5 (15)
Bradycardia	1.3 (1)
PEA/EMD	7.8 (6)
Unknown	5.2 (4)

Total n = 77.
IQR = interquartile range; GOS = Glasgow Outcome Scale; PEA = pulseless electrical activity; EMD = electromechanical dissociation.

Statistical analysis. The primary endpoint was analyzed with descriptive statistics on the basis of 2 × 2 table with SSEP during hypothermia and normothermia as absent or present. The secondary endpoint was identically analyzed with SSEP during hypothermia and poor neurologic outcome as absent or present. Positive predictive values with their 95% confidence intervals (CI) were calculated.

RESULTS Seventy-eight patients were included. One patient was excluded because he was diagnosed with a subarachnoid hemorrhage. None of the patients were lost to follow-up. The baseline characteristics and neurologic outcome are summarized in table 1. Thirty days after admission, 51 patients (66%) had a poor neurologic outcome (GOS 1–2).

Table 2 Results of median nerve somatosensory evoked potentials (SSEP) during hypothermia and normothermia

	Values
SSEP during hypothermia	77
Body temperature, °C, median (IQR)	32.7 (32.5–33.4)
N20 Present, % (n)	80.5 (62)
N20 Absent, % (n)	16.9 (13)
N20 Indeterminable, % (n)	2.6 (2)
Time from resuscitation to SSEP during hypothermia, h, median (IQR)	20 (14–24)
SSEP during normothermia	34
Body temperature, °C, median (IQR)	37.0 (36.3–37.4)
N20 Present, % (n)	64.7 (22)
N20 Absent, % (n)	29.4 (10)
N20 Indeterminable, % (n)	5.9 (2)
Time from resuscitation to SSEP during normothermia, h, median (IQR)	63 (49.5–90.5)

IQR = interquartile range.

The results of the SSEP are shown in table 2. A total of 111 SSEP were performed, 77 during hypothermia and 34 during normothermia. Two hypothermic SSEP were undeterminable, due to technical shortcomings. Therefore, hypothermic SSEP results of 75 patients were available for analysis. Median (interquartile range) duration from resuscitation to hypothermic SSEP was 20 (14–24) hours, to normothermic SSEP 63 (49.5–90.5) hours. The hypothermic SSEP was absent in 13 patients (17%). Three of these 13 patients died before a repeated SSEP could be performed. Therefore, in 10 patients the SSEP was repeated during normothermia. One patient had an undeterminable result. The remaining 9 SSEP showed a bilaterally absent cortical N20 response in all, yielding a positive predictive value for the absence of SSEP after rewarming of 1.00 (95% CI 0.70–1.00, table 3). All 13 patients with an absent hypothermic SSEP had a poor neurologic outcome, yielding a positive predictive value of 1.00 (95% CI 0.77–1.00, table 4). In 24 of the 62 patients with a present hypothermic SSEP, a normothermic SSEP was performed; 1 was undeterminable. The remaining 38 patients regained consciousness (n = 22) or died (n = 16) before a normothermic SSEP could be performed. In 1 patient the SSEP was present during hypothermia, but absent during normothermia. There was no significant difference in body temperature in patients with a present or absent SSEP in both groups.

Table 3 Results of median nerve somatosensory evoked potentials (SSEP) during hypothermia vs normothermia

	Normothermia		
	Absent SSEP	Present SSEP	Total
Hypothermia			
Absent SSEP	9	0	9
Present SSEP	1	22	23
Total	10	22	32

Positive predictive value of absent hypothermic SSEP for absent normothermic SSEP 1.00 (95% confidence interval 0.70–1.00).

Table 4 Results of median nerve somatosensory evoked potentials (SSEP) during hypothermia vs neurologic outcome

	Poor outcome	Good outcome	Total
Absent SSEP	13	0	13
Present SSEP	36	26	62
Total	49	26	75

Positive predictive value of absent hypothermic SSEP for poor outcome 1.00 (95% confidence interval 0.77–1.00).

DISCUSSION The results of this study show that bilateral absence of the cortical N20 response of median nerve SSEP during hypothermia seems to be a good predictor for absent cortical N20 responses after rewarming. An absent SSEP during hypothermia may diminish uncertainty in family members and allow them to get accustomed to the idea that their beloved one will not wake up again. It also may lead to implementation of treatment restrictions. In normothermic comatose survivors after CPR, the bilateral absence of cortical N20 responses of the SSEP has been shown to correlate invariably with a poor neurologic outcome and in the Netherlands a bilaterally absent SSEP in normothermic patients leads to the withdrawal of supportive treatment.[1,2] Our results also show that the patients with an absent SSEP during hypothermia always had a poor neurologic outcome. In one patient the cortical N20 response was present during hypothermia, but absent after regaining normal body temperature, when the SSEP was repeated because of persisting coma. This SSEP during hypothermia was performed only 4 hours after CPR. A possible explanation for this phenomenon might be ongoing cerebral injury after resuscitation with enhanced neuronal damage. The pathophysiology of postanoxic encephalopathy is not completely understood. It has been hypothesized that after a short period of hyperperfusion after successful CPR, there is 1.5–12 hours of "delayed hypoperfusion phase" with only 50% of normal cerebral

blood flow.[8] This phase causes secondary ischemia, which leads to additional cerebral necrosis. The PROPAC study also reported 9 patients with initially present SSEP and an absent SSEP in a later recording.[2] All these patients had a poor neurologic outcome.

A limitation of our study is the relatively small number of bilaterally absent SSEP (13/75, 17%) during hypothermia. In another study, median nerve SSEP were performed 24–28 hours after CPR in 60 consecutive patients (30 in hypothermia group, 30 in normothermia group).[9] In this study, only 3/30 SSEP in the hypothermia group were absent and all 3 patients had a poor neurologic outcome.

Another limitation might be timing of SSEP during hypothermia, which is often performed within 24 hours. Previous studies showed that within 24 hours after CPR, latency of the cortical N20 response can be prolonged and an absent SSEP can be correlated with a good neurologic outcome in isolated cases.[10,11] However, in 3 series including 242 patients, 94 patients with bilaterally absent cortical N20 responses of SSEP recorded within 40 minutes to 24 hours after return of spontaneous circulation in patients after CPR invariably had a poor neurologic outcome.[12,13,14] Therefore, literature strongly supports the prognostic value of an early absent SSEP after CPR. In this study, 75% of the hypothermic SSEP were performed within 24 hours and in hypothermic conditions, but the bilateral absence of cortical N20 responses remains a reliable predictor of poor neurologic outcome.

The hypothesis of the possible reliability of the results of SSEP during body temperature between 32°C and 34°C was based on previous literature. Hypothermia is known to prolong the latency, due to slowing of nerve conduction along axons and synaptic delay, because of decreased membrane potential.[15-20] At lower temperatures conduction velocity in median nerve is likely to decrease 2 m/s/°C.[21] Significant lower nerve conduction velocities and longer latencies of the cortical N20 responses have been found in patients treated with hypothermia after CPR, compared to normothermia.[9] The cortical N20 response disappears with body temperatures between 14.5°C and 29.6°C.[20,22,23] However, the exact effect of temperature on SSEP results remains unclear. Many factors, such as rate of cooling, site of measuring temperature, and range of hypothermia may influence the correlation between decreasing temperature and increasing SSEP latencies. The influence of hypothermia on the amplitude of the cortical N20 response has been reported as variable with tendency to decrease with decreasing temperature.[15,17,19,23] In this study, SSEP latencies and amplitudes were not analyzed.

In the 2 contributing hospitals, more liberal criteria for treatment with hypothermia after CPR are used compared to strict criteria of the previously mentioned international guidelines.[5,6] By including all patients in whom the treating physician decided to treat with hypothermia, regardless of the initial rhythm or the cause of cardiac arrest, the results of this study apply for the daily clinical situation in most Dutch hospitals (survey Bouwes et al., unpublished data).

The Practice Parameter of the American Academy of Neurology "Prediction of outcome in comatose survivors after cardiopulmonary resuscitation" advises to use the median nerve SSEP 24–72 hours after CPR to predict poor neurologic outcome.[24] This advice was based on research in patients with a normal body temperature, but our data show that the SSEP can probably also be used during hypothermia.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by J.M. Binnekade.

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DISCLOSURE

Dr. Bouwes and Dr. Binnekade report no disclosures. Dr. Zandstra serves on the editorial board of *The Netherlands Journal of Critical Care*. Dr. Koelman reports no disclosures. Dr. van Schaik serves on scientific advisory boards for the Sanquin Blood Supply Foundation and the Dutch Bloodbank; serves on the editorial board of the Cochrane Neuromuscular Disease Group; receives honoraria for lecturing and consultancy from Actelion Pharmaceuticals Ltd.; and receives research support from Actelion Pharmaceuticals Ltd., The Netherlands Organisation for Scientific Research [940-33-024 (PI) and 903–51-201 (PI)], and from Prinses Beatrix Fonds [MAR01-0213 (PI)]. Dr. Hijdra receives royalties from publishing *Neurologie* (Elsevier/Bunge, Maarssen 2003). Dr. Horn has received research support from the Netherlands Heart Foundation [2007B039].

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