Cognitive and Neurophysiological Outcome of Cardiac Arrest Survivors Treated With Therapeutic Hypothermia

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Background and Purpose—Cognitive deficits are common in survivors of cardiac arrest (CA). The aim of this study was to examine the effect of therapeutic hypothermia after CA on cognitive functioning and neurophysiological outcome.

Methods—A cohort of 70 consecutive adult patients resuscitated from out-of-hospital ventricular fibrillation CA were randomly assigned to therapeutic hypothermia of 33°C for 24 hours accomplished by external cooling or normothermia. Neuropsychological examination was performed to 45 of the 47 conscious survivors of CA (27 in hypothermia and 18 in normothermia group) 3 months after the incident. Quantitative electroencephalography (Q-EEG) and auditory P300 event-related potentials were studied on 42 patients at the same time point.

Results—There were no differences between the 2 treatment groups in demographic variables, depression, or delays related to the resuscitation. No differences were found in any of the cognitive functions between the 2 groups. 67% of patients in hypothermia and 44% patients in normothermia group were cognitively intact or had only very mild impairment. Severe cognitive deficits were found in 15% and 28% of patients, respectively. All Q-EEG parameters were better in the hypothermia-treated group, but the differences did not reach statistical significance. The amplitude of P300 potential was significantly higher in hypothermia-reated group.

Conclusions—The use of therapeutic hypothermia was not associated with cognitive decline or neurophysiological deficits after out-of-hospital CA. **(*Stroke*. 2007;38:2303-2308.)**

Key Words: cardiac arrest ■ cognition ■ hypothermia ■ P300 evoked response ■ Q-EEG

Cardiac arrest (CA) results in global cerebral ischemia and hypoxic-ischemic injury (HIE). The neuropsychological sequelae of HIE has been reported to comprehend disturbance of memory, including amnestic syndrome, variable executive deficits, changes of personality and behavior, visuospatial deficits, and impairment of expressive language.[1]

In the prospective study of Roine et al with 68 subjects, 60% of conscious survivors of CA had moderate to severe cognitive deficits 3 months after the incident.[2] At 12 months (54 subjects), moderate to severe cognitive deficits were still present in 48% of survivors. In the study of van Alem et al with 57 subjects, 11% to 28% of survivors of out-of-hospital CA were found to be impaired in cognitive functioning at 6 months after the CA, depending on the test.[3] This study did not include patients treated with hypothermia. One study with 35 subjects focusing on memory deficits found moderate to severe memory impairment in 37% of survivors at 7 months after CA.[4]

Quantitative electroencephalography (Q-EEG) and P300 event-related potential have been studied in various disorders of brain function with cognitive impairment, especially in dementing illnesses and mild cognitive decline.[5] Q-EEG uses computer software to provide topographic analysis of brain activity. In experimental animal studies, Q-EEG has also been used to quantify the early cerebral dysfunction after CA.[6] P300 potential can be recorded from brain during the performance of various cognitive tasks. In patients with cognitive impairment the latency to this response is increased and the amplitude of the response is decreased.[7] Auditory evoked P300 potential has also been studied as a prognostic tool for awakening from nontraumatic coma.[8]

Therapeutic hypothermia of 33°C administered for 12 to 24 hours after CA increases the proportion of patients with neurologically good outcome.[9,10] In 1 study therapeutic hypothermia also increased the chance of survival, and the lower mortality rate was not associated with increased disability.[9]

The aim of this randomized prospective study was to examine the effect of therapeutic hypothermia of 33°C after CA on cognitive functioning and neurophysiological outcome with Q-EEG and event-related P300 potential.

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Subjects and Methods

The protocol and consent procedure of this study was approved by the ethics committee of Helsinki University Hospital in accordance with institutional guidelines. A deferred consent was used for all patients. The patient's family had the possibility to withdraw the patient anytime from the study. Patients were informed about the trial both orally and in writing, when they were able to receive this information.

Patients randomized into the Hypothermia After Cardiac Arrest (HACA) trial and surviving for at least 3 months were included.[9] We have previously published the data of serum neuron-specific enolase (NSE) and S-100B in these patients.[11] All adult patients admitted to the emergency department of Helsinki University Hospital after resuscitation from out-of-hospital CA between March 1st 1997 and June 30th 2000 were screened for the trial. The inclusion criteria were an age of 18 to 75 years, a witnessed CA with ventricular fibrillation or nonperfusing tachycardia as the initial cardiac rhythm, a presumed cardiac origin of the arrest, an estimated interval of 5 to 15 minutes from the patients collapse to the first resuscitation attempt by emergency medical personnel, and an interval of less than 60 minutes from collapse to restoration of spontaneous circulation (ROSC). Patients responding to verbal command after ROSC were excluded. Additional exclusion criteria have been previously described.[9] CA was defined as the absence of both palpable pulse and spontaneous respiration. ROSC was defined as return of palpable arterial pulse. All CA data were collected according the Utstein style.[12]

All patients were treated in the Intensive Care Unit (ICU). Patients randomized to normothermia were allowed to rewarm passively to normothermia (core temperature $<38°C$) and were then kept normothermic by physical and antipyretic means. Those randomized to hypothermia treatment were actively cooled externally to a core temperature $33\pm1°C$ with a cooling device (Therakool Kinetic Concepts Inc, United Kingdom). Hypothermia of $33\pm1°C$ was maintained for 24 hours from start of cooling and patients were then allowed to rewarm slowly over 12 hours, aiming at warming rate not exceeding 0.5°C. The temperature was measured from urinary bladder using a Foley catheter with a temperature sensor. The protocol for the ICU treatment has been previously described.[11] Brain imaging with computerized tomography (CT) was performed on clinical basis to patients not recovering consciousness during the first 3 to 5 days and to conscious patients with focal neurological findings.

Assessment of Outcome

Neurological examination was performed daily at the ICU, on days 3, 7, and 14, at discharge from hospital, at 3 months, and at 6 months after CA. At day 14, The Mini Mental State Examination (MMSE) was performed by 1 investigator to all patients able to communicate verbally. The outcome at 3 and 6 months after CA was assessed by the Pittsburgh Outcome Scale.[12,13] This is a 5-category scale of cerebral performance categories (CPC): CPC 1, conscious and alert with normal cerebral function; CPC 2, conscious and alert with moderate cerebral function; CPC 3, conscious with severe cerebral disability; CPC 4, comatose or in persistent vegetative state; CPC 5, dead.

Assessment of Cognitive Function

Comprehensive neuropsychological examination was performed 3 months after the CA. In statistical analyses a reduced amount of test variables was used and grouped according to 3 functional domains. A general cognitive capacity was estimated by the Information subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R).[14] Learning and memory domain was evaluated by immediate and delayed retrieval of logical memory test from the Wechsler Memory Scale-Revised (WMS-R),[15] the 5th retrieval score and 20 minute delayed reproduction score of the Auditory Verbal Learning Test (AVLT), and by picture recognition task of the Rivermead Behavioral Memory Test.[16] Executive functioning was measured with the Interference task of the modified Stroop test (50 items), the Trail-Making test (form B), verbal fluency-task (one minute generation of words beginning with letter K), and with a timed calculation task.[16] Speed of performance was estimated with Digit symbol subtask of the WAIS-R, the Trail-Making test (form A), Color naming of the modified Stroop test (50 items), and with the Grooved Pegboard task (dominant hand score).[16] Depressive symptoms were evaluated by a short form of the Beck Depression Inventory.[17] The neuropsychologist who examined the patients was blinded for the treatment group.

In addition to group analyses, cognitive deficit scores were calculated using age corrected normative data derived from the Finnish population norms. Memory tests available for the deficit score analysis were immediate and delayed retrieval of the WMS-R.[15,18] Deficit scores for executive function were derived from the Trail-Making-form B, interference part of the modified Stroop test and verbal fluency task[19–21] and for speed of performance form the Trail-making-Form A, naming part of the modified Stroop task and Digit Symbol task of the WAIS-R.[14,20,21] The cut point of 1.5 standard deviation (SD) below the normative data were used as a criterion for an impaired cognitive performance in a particular test. Patient's performance was considered intact or containing only subtle cognitive deficits if more than 70% (6 out of 8 tests) of the test scores were above cut point. Moderate impairment meant that 30% to 60% of the tests (3 to 4 tests) were below the cut point, and severe impairment was determined when more than 60% (5 to 8 tests) of the tests were below the cut point. Cognitive functions were considered impaired if half of the tests measuring a particular domain were below the cut point.

Measurement of Q-EEG and P300 Auditory-Evoked Potential

The recordings were performed in a quiet and dim room. The subjects lied in a comfortable bed, kept their eyes closed, and were reminded to stay awake. EEG was recorded with 21 channels. For quantitative analysis, 24 epochs lasting 2.5 seconds each were gathered. The chosen epochs had to be artifact-free and without signs of lowered level of vigilance in the EEG or electro-oculographic channels during the recording. The analyzed frequency band was divided into delta (1.5 to 3.5 Hz), theta (3.5 to 7.5 Hz), alpha (7.5 to 12.5 Hz), and beta band (12.5 to 25.0 Hz). In monopolar montages (A1A2 as reference), absolute and relative power values were analyzed in the above mentioned bands in all 21 channels. The mean frequencies within the whole 1.5 to 25 Hz frequency band were analyzed in all channels. The number of variables was reduced by calculating regional means from the original variables: frontal region (Fp1, Fp2, Fpz, F3, F4, Fz), temporal region (T3, T4, T5, T6), centroparietal region (C3, C4, Cz, P3, P4, Pz), and occipital region (O1, O2, Oz) by a method previously described.[22] After these calculations there were 36 EEG variables (16 for the absolute power, 16 for the relative power, and 4 for mean frequencies).

For P300, the stimulation frequency was 0.50 to 0.58 Hz. Tones were presented binaurally, with the standard tone frequency 1000 Hz, and the target tone frequency 2000 Hz. Two 256-trial blocks were presented, each containing 64 (25%) target stimuli in a random order. The subjects were instructed to count silently the number of the targets. Activity was recorded at Cz and Pz electrode sites of the 10 to 20 International System, referred to linked earlobes. The filter bandpass was 0.5 to 70 Hz. The analysis time was 650 ms including a 50 ms prestimulus baseline. Latencies and amplitudes were measured afterward using a method previously described.[22] The neurophysiologist analyzing the Q-EEGs and P300 potentials was unaware of the treatment assignment.

Statistical Analysis

Categorical variables are given as counts and percentages. Data are given as mean and SD. Cognitive functions were analyzed with MANOVAs and subsequent ANOVAs. Other continuous data were compared with the *t* test or Mann-Whitney *U* test. The neurological outcome was dichotomised into good (CPC 1 and 2) or poor (CPC 3, 4, and 5) and χ^2 test was used to compare proportions between hypothermia and normothermia groups. Correlations were analyzed

TABLE 1. Demographical and Clinical Characteristics of Neuropsychologically Studied Patients

	Hypothermia (n=27)	Normothermia (n=18)	*P* Value
Age, years	59 (11.4)	55 (14.5)	0.251
Male/female, n (%)	25/2 (93/7)	14/4 (78/12)	0.325
Years of education (2–6)	3.4 (1.5)	3.0 (1.5)	0.467
VIQ	104.2 (20.4)	102.9 (20.6)	0.848
Beck's Depression Inventory (short form)	3.4 (3.4)	4.9 (5.0)	0.271
Bystander initiated CPR, n (%)	12 (44)	12 (67)	0.143
BLS, min	7 (2.3)	6 (2.0)	0.417
ACLS, min	15 (6.9)	14 (9.1)	0.242
ROSC, min	17 (5.8)	15 (4.6)	0.281
Glasgow Coma Scale on admission	5 (0.8)	5 (1.3)	0.138
Tympanic temperature on admission, °C	35.5 (0.8)	35.3 (0.8)	0.517
Blood glucose on admission, mmol/L	9.6 (2.9)	9.9 (3.5)	0.790
Thrombolysis, n (%)	11 (44)	6 (33)	0.616
Acute myocardial infarction, n (%)	18 (67)	10 (56)	0.451
Ischemia without infarction, n (%)	5 (19)	2 (11)	0.502
Primary arrhythmia, n (%)	4 (15)	6 (33)	0.143
Diabetes, n (%)	1 (4)	2 (11)	0.329
Serum NSE at 24 hours after CA, μg/L	12.2 (6.9)	9.9 (8.4)	0.010*
Serum NSE at 48 hours after CA, μg/L	9.3 (6.0)	9.0 (10.4)	0.219
MMSE at day 14 after CA	25 (3.8, n=20)	22 (7.5, n=16)	0.135
CABG or PCI, n (%)	16 (64)	7 (39)	0.181

Data are given as mean and SD or No. and percentage. VIQ indicates Verbal Intelligence Quotient (estimated from the Information subtest of the WAIS-R); CPR, cardiopulmonary resuscitation; BLS, basic life support; ACLS, advanced cardiac life support; ROSC, restoration of spontaneous circulation; NSE, neuron-specific enolase; CA, cardiac arrest; MMSE, Mini Mental State examination; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

using Spearman rho test. Probability values <0.05 were considered as statistically significant. We used SPSS 13.0 data analysis software system (SPSS Inc) to analyze the data.

Results

Seventy consecutive unconscious (Glasgow Coma Scale <9) patients met the HACA-inclusion criteria and were randomly assigned to hypothermia (n=36) or normothermia (n=34) treatment. At 3 months after CA, 50 of them (28 in hypothermia group and 22 in normothermia group, $P=0.226$) were alive. None of the patients primarily discharged to home or rehabilitation center died during the 6-month follow-up time. Three patients (1 in hypothermia group and 2 in normothermia group) were unconscious at 3 months after CA. Two normothermia group patients (CPC 1 and CPC 2) were unable to attend the neurological studies because of long distances. Both of them lived alone and were independent in all ADL-functions, according to themselves and their closest relatives.

Neuropsychological testing 3 months after the CA was thus performed to 45 survivors (27 in hypothermia group and 18 in normothermia group). The clinical characteristics, education, and verbal intelligence quotient of the tested patients are presented in the Table 1. Statistically the 2 treatment groups were comparable, although the level of serum NSE at 24 hours after CA was slightly higher and the resuscitation delays tended to be longer in the hypothermia group. Brain CT had been performed to 8 patients (30%) in hypothermia group and 10 patients (56%) in normothermia group during the hospitalization. The CT findings were insignificant. In hypothermia group the CT showed an ischemic lacunar stroke in 2 patients and a small traumatic cerebellar hemorrhage (diameter 1 cm) in 1 patient. In normothermia group the CT revealed a lacunar ischemic stroke in 2 patients. Only 1 of the studied patients (in hypothermia group) experienced a major neurological complication after recovery of consciousness. This patient had a secondarily generalized status epilepticus and had later severe cognitive deficits in the neuropsychological examination.

In hypothermia group 25 of the tested 27 patients (93%) had achieved good outcome (CPC 1: 19; CPC 2: 6) and 2 patients had CPC 3 at 3 months after CA. In normothermia treated group 14 of the tested 18 patients (78%) had achieved good outcome (CPC 1: 10; CPC 2: 4) and 4 patients had CPC 3.

At the time of the examination, 25 patients in the hypothermia treated group and 15 patients in the normothermia treated group lived at home (93% and 83%, respectively). Only 1 patient lived alone, all other patients lived with their spouse or other close relative. 5 patients (2 in hypothermia and 3 in normothermia group) were in institutional care at 3 months after CA; at 6 months 4 patients still needed long-term institutional care (1 and 3 patients, respectively). At 6

TABLE 2. Cognitive Performance Three Months After Cardiac Arrest

Cognitive Functions	Hypothermia (n=27)	Normothermia (n=18)	*P* Value
Learning and memory*			0.446
WMS-R, logical memory (passage I)			
Immediate (max 25)	8.80 (3.15)	8.56 (4.43)	0.836
Delayed (max 25)	6.22 (3.58)	6.47 (5.36)	0.854
AVLT, 5. retrieval (max 15)	9.0 (3.10)	9.7 (3.14)	0.458
AVLT, delayed (20 minutes)	6.84 (3.56)	6.45 (4.14)	0.743
RBMT, pictures (max 10)	9.1 (2.1)	8.4 (2.6)	0.304
Executive functioning*			0.605
Stroop, interference, sec	88.70 (43.90)	89.15 (30.98)	0.970
Trail-Making B, sec	163.33 (80.60)	169.43 (128.38)	0.845
Verbal fluency, letter K (1 minute)	14.93 (6.17)	12.72 (4.95)	0.212
Simple calculation, sec	118.12 (66.37)	136.94 (82.97)	0.404
Speed of performance*			0.151
WAIS-R/Digit symbol	30.89 (11.76)	28.25 (12.17)	0.491
Trail-Making A, sec	54.96 (22.87)	72.06 (54.26)	0.163
Stroop, naming, sec	45.54 (16.20)	46.56 (15.79)	0.841
Grooved Pegboard (dom), sec	90.42 (27.58)	81.12 (19.36)	0.245

Data are given as mean and SD. Please see text for the abbreviations.
*Manova followed by Anovas for each tests.

months after CA, 7 patients in hypothermia group had returned to their previous employment, 1 patient was still on sick-leave, and 3 patients had retired from their previous work because of the event. In normothermia group 6 patients had returned to their previous work and 6 patients were retired.

Neuropsychological Results

The neuropsychological performance of the 2 treatment groups is presented in the Table 2. Statistically significant differences were not found in any of the cognitive functions between the 2 groups. Analyses with the cognitive deficit scores revealed severe cognitive deficits in 15% (n=4) of the hypothermia-treated and in 28% (n=5) of the normothermia-treated group. Severe cognitive deficits indicating dementia and permanently affecting activities of daily living were found in 4 patients (2 in both groups). Moderate cognitive deficits were found in 19% (n=5) and 28% (n=5) patients, respectively. 67% (n=18) of hypothermia-treated and 44% (n=8) of normothermia-treated patients were cognitively intact or had only subtle deficits. Although there was a trend to better cognitive outcome in hypothermia group, the differences were not statistically significant. Altogether, 33% of patients had deficits in executive functioning, 24% in learning and memory and 19% in speed of performance. Poor performance in all measured cognitive functions correlated significantly with high CPC-values at 3 and 6 months after CA ($P<0.01$). There was no correlation between cognition and resuscitation delays.

Q-EEG and P300

Of the 45 patients tested neuropsychologically, 3 patients (all in institutional care) refused or were not eligible for the recording of Q-EEG and P300 potential. Thus Q-EEG and P300 could be performed to 42 patients (26 in hypothermia and 16 in normothermia group). One Q-EEG recording failed because of technical artifact, and 2 P300 recordings failed because of patient-related difficulties. There were no statistically significant differences in the Q-EEG parameters between the treatment groups, although Q-EEGs of hypothermia group patients included consistently more fast and less slow frequency activity in all brain regions. There were no consistent correlations between single Q-EEG parameter values and cognitive performance. The results of P300 recordings are presented in the Table 3. The Q-EEG or P300 variable values did not correlate with the resuscitation delays.

The P300 amplitude correlated with the CPC-class at 3 ($r=-0.37$, $P=0.016$) and at 6 months ($r=-0.51$, $P=0.001$) after CA. The P300 amplitude correlated with all tests measuring speed of performance: Digit Symbol subtest of the WAIS-R ($r=-0.41$, $P=0.009$), Trail-Making A ($r=0.32$, $P=0.044$), Stroop naming ($r=0.52$, $P=0.001$), and Grooved Pegboard test ($r=-0.32$, $P=0.043$); with 2 of the 4 measures of executive functioning: Stroop Interference task ($r=0.53$,

TABLE 3. Auditory Evoked P300 Potential

	Hypothermia (n=26)	Normothermia (n=14)	*P* Value
Latency to P300 response, ms	374.4 (42.5)	385.6 (43.4)	0.453
Amplitude of P300 response, μV	7.91 (5.12)	4.99 (2.99)	0.028

Data are given as mean and SD.

$P=0.0001$) and Verbal fluency task ($r=0.44$, $P=0.004$); and with 2 of the 5 tasks measuring learning and memory: 5th retrieval and delayed retrieval of the AVLT ($r=0.38$, $P=0.017$; $r=0.47$, $P=0.003$, respectively). As expected, the latency of P300 correlated with age ($r=0.40$, $P=0.006$). Furthermore, the correlation between P300 latency and cognitive performance was found in all but 1 tests measuring speed of performance: Trail-Making A ($r=0.33$, $P=0.029$); Stroop naming ($r=0.49$, $P=0.001$), and Digit Symbol subtask of the WAIS-R ($r=-0.38$, $P=0.011$); with half of the tests of executive functioning: Stroop Interference task ($r=0.35$, $P=0.022$) and Verbal fluency task ($r=0.42$, $P=0.004$); and with 1 task of learning and memory: delayed retrieval of the AVLT ($r=-0.37$, $P=0.009$).

Discussion

In our study mild therapeutic hypothermia of 33°C for 24 hours after out-of-hospital ventricular fibrillation CA had no negative effect on cognition. 67% of the survivors in hypothermia group and 44% of those in normothermia group were cognitively intact or had only subtle cognitive deficits, but this difference was not statistically significant. The amplitude of the P300 response was significantly higher in the hypothermia treated group.

The results of the neuropsychological tests in our study are mostly in accordance with previous prospective studies.[2,3] However, in our study the most commonly impaired cognitive domain was executive functioning, followed by memory and learning. This can be explained by the fact that in previous studies memory functions have been studied more extensively than executive functions. In most patients referred to neuropsychological examination for memory deficits the cognitive impairment is a combination of memory and executive and mild motor deficits.[23] Cognitive impairment is not uncommon after surviving a critical illness. A recent study examining cognitive performance and specifically executive function in a population of general intensive care survivors found these functions to be very significantly impaired at least three months after discharge from ICU.[24]

Grubb et al reported a correlation between resuscitation delays and memory impairment,[4] but the prospective study of Roine et al[2] did not find a similar correlation, and the prospective study of van Alem et al[3] reported only a weak correlation. It thus seems that long delays in the resuscitation do not exclude the possibility of good cognitive outcome.[3] In our study cognition did not correlate with the resuscitation delays, nor did any of the Q-EEG variables or the latency or amplitude of the P300 response. Instead, most of the measured cognitive variables correlated with P300 response and with CPC-outcome.

There are some limitations of this study. Although we did examine all except 2 patients alive and conscious at this time point, the sample size remains relatively small. The absence of statistically significant differences between the treatment groups could be related to the sample size. The majority of the studied patients reached a good outcome, which may partly explain the absent association between resuscitation delays and neuropsychological and neurophysiological test results. The neuropsychological testing was performed 3 months after CA, earlier than in the study of van Alem et al.[3] This time point was selected to exclude the habituation effect, as neuropsychological rehabilitation for selected patients was not started until after this time point. It is possible that some patients would have spontaneously improved over the next months. However, dramatic spontaneous changes of cognitive performance between 3 and 12 months after CA are uncommon. In the study of Roine et al, 23% of patients showed mild overall improvement between the 3 and 12 months tests, whereas 8% of patients showed mild overall decline.[2] In the study of Drysdale et al, the memory impairment detected at 8 months after CA did not show signs of improvement during 3 years follow-up.[25]

Comprehensive neuropsychological and neurophysiological findings in CA survivors treated with therapeutic hypothermia have not been previously reported. According to our results, the use of therapeutic hypothermia was not associated with cognitive decline and neurophysiological deficits after out-of-hospital CA. Even though the small sample size limits the interpretation of the results, we found no evidence that the previously reported increase in survival rate would be translated to clinically significant cognitive deficits.

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Disclosures

None.

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