THERAPEUTIC HYPOTHERMIA AFTER CARDIAC ARREST

Studies on neurological and cardiological outcome and prediction of outcome in hypothermia-treated patients resuscitated from out-of-hospital cardiac arrest

MARJAANA TIAINEN

ACADEMIC DISSERTATION

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REFERENCES

ORIGINAL PUBLICATIONS
This thesis is based on the following publications, which will be referred to in the text by their Roman numerals:


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In addition, some unpublished data are presented.
ABBREVIATIONS

ACLS  Advanced cardiac life support
aEEG  Amplitude-integrated electroencephalography
ATP  Adenosine triphosphate
BAEP  Brain stem auditory evoked potential
BLS  Basic life support
BNP  Brain natriuretic peptide
CA  Cardiac arrest
CABG  Coronary artery bypass grafting
CI  Confidence interval
CPC  Cerebral performance category
CPR  Cardiopulmonary resuscitation
CSF  Cerebrospinal fluid
CT  Computerized tomography
ECG  Electrocardiography
EEG  Electroencephalography
EF  Ejection fraction
EMS  Emergency medical service
HACA  Hypothermia after cardiac arrest
HF  High frequency
HIE  Hypoxic-ischemic encephalopathy
HRV  Heart rate variability
ICD  Implantable cardioverter defibrillator
ICP  Intracranial pressure
ICU  Intensive care unit
I.V.  Intravenous
LF  Low frequency
MCA  Median cerebral artery
MI  Myocardial infarction
MMN  Mismatch negativity
MRI  Magnetic resonance imaging
NNT  Number-needed-to-treat
NSE  Neuron-specific enolase
OPC  Overall performance category
OR  Odds ratio
PCI  Percutaneous coronary intervention
PEA  Pulseless electrical activity
PVB  Premature ventricular beat
pNN50  Relative number of normal-to-normal (NN) intervals differing by more than 50 ms from the immediately preceding NN interval of the ECG

Q-EEG  Quantitative electroencephalography

rMSSD  Root mean square of successive NN differences in an ECG

ROC   Receiver operating characteristics

ROSC  Restoration of spontaneous circulation

SDANN Standard deviation of the averaged NN intervals for all 5-minute periods of the 24-hour ECG recording

SDNN  Standard deviation of individual NN intervals of the ECG

SEP   Sensory evoked potential

SVPB  Supraventricular premature beat

S-100B S-100B protein

VF    Ventricular fibrillation

VT    Ventricular tachycardia
ABSTRACT

Background

The outcome of the successfully resuscitated patient is mainly determined by the extent of hypoxic-ischemic cerebral injury. Hypothermia has multiple mechanisms of action in mitigating such injury. It reduces the metabolic rate and oxygen consumption, diminishes excitotoxic action, suppresses the production of superoxide anions, nitric oxide and various cytokines, and maintains the integrity of the blood-brain barrier.

Early prediction of neurological outcome in patients resuscitated from cardiac arrest (CA) is a challenging task. To avoid a falsely pessimistic prognosis, tests used in critical care are required to have high specificity for poor outcome, with less emphasis on sensitivity. High serum levels of neuron-specific enolase (NSE) and S-100B protein are associated with ischemic brain injury and poor outcome after CA. The median nerve somatosensory evoked potentials (SEPs) accurately predict poor outcome after CA. The prognostic value of serum NSE and S-100B protein and SEPs have not, however, been studied in CA patients treated with hypothermia.

The present study was undertaken from 1997 to 2001 in Helsinki as a part of the European multicenter study “Hypothermia after cardiac arrest” (HACA) to test the neuroprotective effect of therapeutic hypothermia in patients resuscitated from out-of-hospital ventricular fibrillation (VF) CA. The aim of this substudy was to examine the neurological and cardiological outcome of these patients, and especially to study and develop methods for prediction of outcome in the hypothermia-treated patients.

Patients and methods

A total of 275 patients were randomized to the HACA trial in Europe. All adult patients admitted to the emergency department of Helsinki University Central Hospital after resuscitation from out-of-hospital CA from March first 1997 to June thirtieth 2000 were screened for the trial. In Helsinki, 70 patients were enrolled in the study according to the inclusion criteria. Of those 70, 36 patients were randomized to hypothermia treatment and 34 patients to normothermia treatment.

Those randomized to hypothermia were actively cooled externally to a core temperature 33 ± 1°C with a cooling device. Hypothermia was maintained for 24 hours. All patients received standard intensive care management and monitoring at the Intensive Care Unit (ICU) of Meilahti Hospital.

Serum NSE and S-100B were sampled at 24, 36, and 48 hours after CA.
The SEPs and brain stem auditory evoked potentials (BAEPs) were recorded 24 to 28 hours after CA from 60 consecutive patients; 24-hour ambulatory electrocardiography (ECG) recordings were performed at 0 to 24 hours, at 24 to 48 hours, and at 14 days. Arrhythmias and heart rate variability (HRV) were analyzed from the tapes. The clinical outcome was assessed 3 and 6 months after CA by the Pittsburgh Outcome Scale and dichotomized into good or poor. Neuropsychological examinations were performed on 45 of the 47 conscious survivors of CA 3 months after the incident. Quantitative electroencephalography (Q-EEG) and auditory P300 event-related potentials were studied for 42 patients at the same time-point.

Main results
Therapeutic hypothermia of 33ºC for 24 hours increased the chance of favorable neurological outcome and survival in comatose CA patients resuscitated from VF or non-perfusing ventricular tachycardia (VT). In the multicenter HACA study, 55% (N=75) of hypothermia-treated patients and 39% (N=54) of normothermia-treated patients reached a good neurological outcome (p=0.009) at 6 months after CA. In the hypothermia group 41% (N=56) of patients had died; in the normothermia group the respective figure was 55% (N=76) at 6 months after CA (p=0.020). In Helsinki the outcome was favorable (Cerebral Performance Category (CPC) 1 or 2) in 69% (N=25) of hypothermia-treated patients and in 47% (N=16) of normothermia-treated patients (p=0.057).

Therapeutic hypothermia was well tolerated. The occurrence of premature ventricular beats was higher in the hypothermia-treated group during the first two recordings, with no difference in the number of ventricular tachycardia or VF episodes. All HRV values were significantly higher during the hypothermia (down to p<0.001), but no differences were observed 2 weeks later.

The levels of serum NSE, but not the levels of S-100B, were lower in hypothermia- than in normothermia-treated patients. A decrease in NSE values between 24 and 48 hours was observed in 30 of 34 (88%) patients in the hypothermia group and in 16 of 32 (50%) patients in the normothermia group. The decrease in NSE values was associated with good outcome at 6 months after CA. In SEP recordings the latencies to N13 response and to early cortical N20 response were significantly longer in the hypothermia group. Bilaterally absent N20 waves predicted permanent coma with a specificity of 100% in both treatment arms. BAEP recordings did not correlate with outcome in either treatment group.

At 3 months after CA, no differences appeared in any cognitive functions between the two groups: 67% of patients in the hypothermia and 44% patients in the normothermia group were cognitively intact or had only very mild impairment. 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 the hypothermia-treated group.

Conclusions
Therapeutic hypothermia of 33°C for 24 hours led to an increased chance of good neurological outcome and survival after out-of-hospital VF CA. Use of therapeutic hypothermia was not associated with any increase in clinically significant arrhythmias. In victims of CA, decreasing levels of serum NSE but not of S-100B over time may indicate selective attenuation of delayed neuronal death by therapeutic hypothermia. The time-course of serum NSE between 24 and 48 hours after CA may help in clinical decision-making. Use of therapeutic hypothermia after CA may change or invalidate the prognostic value of serum NSE and S-100B, but the absence of early cortical responses in median nerve SEPs seems to accurately predict permanent coma also in these patients. Recording of BAEPs provided no additional benefit in outcome prediction. Preserved 24- to 48-hour HRV may be a predictor of favorable outcome in CA patients treated with hypothermia.

Use of therapeutic hypothermia was associated with no cognitive decline or neurophysiological deficits after out-of-hospital CA. We found no evidence that the increase in survival rate would be translated to clinically significant cognitive deficits. These results give further support to the use of therapeutic hypothermia in patients with sudden out-of-hospital CA.
Modern basic cardiopulmonary resuscitation (CPR) was created during the 1958 to 1961 period, when artificial respiration was combined with artificial circulation. The first out-of-hospital cardiac arrest (CA) was successfully treated by Claude Beck already in 1955, but true portable direct current defibrillators were not developed until the 1960’s (Eisenberg 1996). The first prehospital emergency cardiac care unit with a physician was set up in Belfast, Ireland, in 1966; and during its first year of activity, the unit successfully resuscitated 10 patients from ventricular fibrillation (VF) CA (Pantridge and Geddes 1967). In Helsinki, the first physician-manned emergency ambulance service began in December 1972, and as this activity became established, research in the field of CA also became active. In the end of the 1980’s, the Helsinki system was developed towards paramedic-manned first-response units. Semi-automatic defibrillators were installed in all ambulances on call in 1989 (Nyström 2005). During the last 5 years, about 170 witnessed CA cases in which CPR was started have occurred in the Helsinki city area every year, and in about 80 to 90 of them, the primary rhythm has been VF or ventricular tachycardia (VT) (M. Kuisma and J. Boyd, personal communication, 2007). The physician-manned emergency helicopter, Medi-Heli, started to operate outside the Helsinki city area in August 1992. Medi-Heli treats annually about 190 cases of witnessed CA in which CPR has been started (J. Virta, personal communication, 2007).

Approximately half of those successfully resuscitated and admitted to hospital die in the hospital, the majority of them due to neurological injury. Most resuscitated patients are initially comatose. Early prediction of outcome in patients resuscitated from CA is a difficult and challenging task. There are very few methods which accurately predict permanent coma, and no tests that would accurately predict good recovery after CA. Early reliable prediction of outcome would not only help the treating physicians to choose optimal treatment, but also would alleviate the anxiety of the patient’s loved ones.

Induced hypothermia was first introduced as a means of cerebral protection during cardiac surgery in 1950 by Bigelow (Bigelow et al 1950a). In the 1950’s, hypothermia was applied for a range of neurological indications (Vandewater et al 1958). The first report of the use of induced hypothermia for neurologic injury after CA was published as early as in 1958 (Williams and Spencer 1958). In man, hypothermia was most often utilized at temperatures between 25 and 30ºC (Vandam and Burnap...
However, the side-effects of moderate to deep hypothermia, such as cardiovascular dysfunction and severe infections, and the limited ability to manage these side-effects led to the withdrawal of this therapy.

Interest in the use of therapeutic hypothermia after CA arose again in the early 1990's, when a dog model demonstrated that mild hypothermia started 15 minutes after CA resulted in significant improvement in neurological outcome (Sterz et al 1991). Preliminary feasibility and safety studies suggested that mild therapeutic hypothermia was well tolerated in humans after CA, and that the side-effects of hypothermia could be managed in modern intensive care units (ICU) (Bernard et al 1997, Yanagawa et al 1998, Nagao et al 2000, Zeiner et al 2000).

The present study was undertaken in the period 1997 to 2001 in Helsinki as a part of the European multicenter study “Hypothermia after cardiac arrest” (HACA) to test the neuroprotective effect of therapeutic hypothermia in patients resuscitated from out-of-hospital VF CA. The aim of this substudy was to examine the cardiological and neurological outcome of these patients, and especially to study and develop methods for the prediction of outcome in these patients.
2 REVIEW OF THE LITERATURE

2.1 Epidemiology and prognosis of cardiac arrest

In Europe, CA occurs in 375 000 patients each year (de Vreede-Swagemakers et al 1997). The incidence of out-of-hospital CA is reported to be between 36 and 128 per 100 000 inhabitants per year in most industrial countries (Becker et al 1991, Becker et al 1993, de Vreede-Swagemakers et al 1997, Herlitz et al 1999, Eisenberg and Mengert 2001, Atwood et al 2005). In Helsinki, the incidence of sudden out-of-hospital CA is about 80/100 000 per year (Kuisma and Määttä 1996).

Of all patients with sudden CA, the primary rhythm is VF in 31 to 65% (Becker et al 1991, Kuisma and Määttä 1996, Eisenberg and Mengert 2001). The incidence of out-of-hospital VF CA has been observed to decrease (Kuisma et al 2001, Herlitz et al 2005), but due to the advances in well-organized emergency medical services (EMS), automated defibrillators and increasing public education, the numbers of comatose CA patients admitted to emergency rooms has increased. Resuscitation is started in 34 to 86% of out-of-hospital CA patients, and in 17 to 49% of them spontaneous circulation can be achieved and the patient admitted to hospital (Roine 2005).

Of those successfully resuscitated and admitted to hospital, about half die in the hospital (Rea et al 2003). Two-thirds of patients dying after primarily successful resuscitation from out-of-hospital CA die due to neurological injury (Laver et al 2004). Survival rates for out-of-hospital CA have ranged from 4 to 33% (Eisenberg and Mengert 2001). Neurological sequelae are usually observed in half the survivors, and are a major cause of mortality and morbidity after primarily successful resuscitation. The proportion of survivors with severe neurologic impairment at hospital discharge ranges from 10 to 40% (Graves et al 1997, Engdahl et al 2003, Wenzel et al 2004). The risk of a persistent vegetative state after CA is relatively low, only 1 to 2% (Roine 1993a, Graves et al 1997), with 5 to 10% of the patients admitted to hospital after primarily successful resuscitation ending in a persistent vegetative state lasting longer than one month (Longstreth et al 1983a). Five-year survival rates among those resuscitated and discharged from hospital range from 50% to nearly 70%. In the USA, the long-term prognosis has improved steadily, whereas in one European study it remained stable (Rea et al 2003, Engdahl et al 2003). In a Norwegian study, the mean survival

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time for patients discharged from hospital alive was 6.13 years, and 23% of patients were alive 10 years after the resuscitation (Naess and Steen 2004). The long-term prognosis of out-of-hospital CA survivors is, however, poorer than that of the gender- and age-matched general population (Rea and Paredes 2004).

2.2 Hypoxic-ischemic encephalopathy

CA results in a temporary interruption or severe reduction in cerebral blood flow. The brain damage following cardiocirculatory arrest is related to the ischemic and hypoxic period and to specific reperfusion disorders. Following global ischemia, the severity of brain damage depends on the duration and severity of the ischemia and on the selective vulnerability of different cell types and brain regions. The most vulnerable neurons are the pyramidal cells in the CA1 and CA4 regions of the hippocampus, neocortical layers 3 to 6, nucleus caudatus, putamen, globus pallidum, the thalamic reticular nucleus, and the cerebellar Purkinje cells (Ross and Graham 1993). The time-course of cell death also differs in different brain regions. Neocortical injury can be detected within a few hours after CA, whereas hippocampal damage occurs in a delayed mode after several days (Petito et al 1987, Horn and Schlote 1992).

Multiple pathophysiological mechanisms are responsible for the brain damage during and after resuscitation. The central element of this cascade is prolonged, excessive influx of Ca²⁺ into the cell. When blood-flow to the brain is interrupted, the levels of high-energy metabolites decrease within seconds. The breakdown of adenosine triphosphate (ATP) and activation of anaerobic glycolysis lead to increased levels of lactate, H⁺ and inorganic phosphates, resulting in intra- and extracellular acidosis. Failure of ATP-dependent Na⁺-K⁺-pumps and K⁺, Na⁺, and Ca²⁺ channels further disturbs the cellular homeostasis and leads to increased influx of Ca²⁺. Ischemia also induces accumulation of excitatory neurotransmitters such as glutamate. This induces a state of permanent excitability, also called an excitotoxic cascade, which can lead to additional cell injury and death (Siesjö et al 1989). The excess Ca²⁺ leads to mitochondrial dysfunction and activation of various intracellular kinases and proteases. It also leads to depolarization of neuronal cell membranes and further release of glutamate into the extracellular space. Specific genes are activated in ischemic conditions, and these genes are very likely involved in the mechanisms of apoptosis (MacManus and Linnik 1997).

Ischemia-induced cell injury is followed by various inflammatory and immunological responses. In global ischemia, this phenomenon is detectable especially during reperfusion. Astrocytes, microglia, and endothelial cells release large quantities of tumor necrosis factor-alpha
and interleukin-1. The increased levels of these pro-inflammatory mediators stimulate accumulation of inflammatory cells in the brain. They also stimulate the appearance of adhesion molecules on leukocytes and endothelial cells. This can lead to synthesis of toxic products, stimulation of further immune reactions, and additional neuronal cell damage (Danton and Dietrich 2003).

Ischemia induces the production of free radicals (superoxide, peroxynitrite, hydrogen peroxide, and hydroxyl radicals), mediators in the transition from cell injury to cell death (Globus et al 1995a). Excessive production of free radicals causes peroxidation of proteins, lipids, and nucleic acids. The fluidity and integrity of cell membranes is impaired by ischemia and reperfusion, and ischemia also results in the disruption of the blood-brain barrier, which may lead to development of edema.

After CA, cerebral microcirculatory reperfusion is impaired, despite adequate systemic hemodynamics. This is related to endothelial cell swelling, increased leukocyte-endothelial interactions, and disseminated intravascular activation of blood coagulation (Fischer and Hossmann 1996, Fischer et al 1996, Böttiger et al 1995, Safar et al 2002). Cerebral autoregulation is impaired in the majority of CA patients in the acute phase (Nishizawa and Kudoh 1996, Sundgreen et al 2001), which is probably related to the early posts ischemic hyperperfusion, which later evolves into multifocal posts ischemic hypoperfusion (Roine et al 1991).

The duration and severity of ischemia are not the only features affecting the severity of brain damage. The presence of hypoxia, hypotension, the level of blood glucose, brain temperature, and the state of precerebral and cerebral arteries also influence the ultimate degree of neuronal injury.

The clinical syndrome related to global cerebral ischemia is called hypoxic-ischemic encephalopathy (HIE). Severe HIE after CA is characterized by coma and a vegetative state of variable duration. Seizures and myoclonus are also common (Roine 2005). Typical neuropathological findings in severe HIE are laminar cortical necrosis, bilateral hippocampal, striatal, and thalamic lesions (Cole and Gowie 1987, Taraszewska et al 2002). Mild to moderate HIE is characterized by a relative scarcity of focal sensomotor deficits, but also occasionally by bibrachial paresis or weakness in all limbs, disturbance of coordination and balance, or dyspraxia or extrapyramidal symptoms. Neuropsychological deficits, ranging from mild deficits in memory and executive functions to severe amnestic syndrome, are common in survivors of CA. At least mild and reversible cognitive deficits can be observed in all CA survivors early after the incident.
2.3 Neuropsychological sequelae and quality of life after cardiac arrest

The neuropsychological sequelae of HIE comprise disturbance of memory, including amnestic syndrome, variable executive deficits, changes in personality and behavior, visuospatial deficits, and impairment of expressive language (Caine and Watson 2000). In the prospective study of Roine et al with 68 subjects, 60% of survivors of CA had moderate to severe cognitive deficits 3 months after the incident; at 12 months after CA (54 subjects), moderate to severe cognitive deficits were still present in 48%. No deficits appeared in 40% and 52% of patients at these respective time-points. Between the 3- and 12-month tests, 23% of patients showed mild overall improvement, whereas 8% of patients showed mild overall decline (Roine et al 1993b). In another prospective study, van Alem et al had 57 subjects, of whom 11 to 28% were impaired in cognitive functioning at 6 months after the CA, depending on the test used. On the other hand, 58% of the patients scored as unimpaired in all tests (van Alem et al 2004a). None of these studies included patients treated with hypothermia.

Isolated amnesia after CA is a rare event; in most patients referred to neuropsychological examination for memory deficits, the cognitive impairment is a combination of memory, executive, and mild motor deficits (Lim et al 2004). One study with 35 subjects focusing on memory deficits in CA survivors found moderate to severe memory impairment in 37% (Grubb et al 1996). The memory impairment in out-of-hospital CA survivors is associated with global reduction in brain volume, not focal hippocampal injury (Grubb et al 2000). In the study of Drysdale et al with 10 subjects, the memory impairment detected at 7 months after CA showed no signs of improvement during 3 years of follow-up (Drysdale 2000). In a cohort study of CA patients resuscitated from out-of-hospital VF, the survivors reported more subjective memory complaints than did a general healthy older population after a median of 4.9 years follow-up (Bunch et al 2004).

Grubb et al reported a correlation between resuscitation delays and memory impairment (Grubb et al 1996), but the prospective study of Roine et al did not find any similar correlation between resuscitation delays and cognition (Roine et al 1993), and the prospective study of van Alem et al reported only a weak correlation (van Alem et al 2004a). It thus seems that long delays in resuscitation do not exclude the possibility of good cognitive outcome.

Most survivors of out-of-hospital CA enjoy a satisfactory quality of life comparable to that of age- and disease-matched controls (Saner et al 2002, Bunch et al 2003, Stiell et al 2003, van Alem et al 2004b, Rea and Paredes 2004). However, one study reported that prevalence of posttraumatic stress
disorder is high, 21 to 35%, among survivors of CA with good neurological outcome, and that survivors with posttraumatic stress disorder experienced impairment in quality-of-life indicators (Gamper et al 2004). Once good neurological outcome has been achieved, it can be maintained for more than 15 years (Harve et al 2007).

2.4 Postresuscitative care

Hypocapnia has been shown to be harmful after CA (Buunk et al 1997) and normocarbia is recommended. Routine hyperventilation should be avoided, since it may induce cerebral ischemia in the postresuscitation period (International consensus on cardiopulmonary resuscitation 2005).

Postarrest hyperthermia is common during the first 48 hours after CA (Takino and Okada 1991, Takasu et al 2001). Because the risk of unfavorable outcome after CA increases with each degree of body temperature higher than 37°C (Zeiner et al 2001), hyperthermia should be avoided. Two randomized clinical trials have shown improved neurological outcome in adults who remained comatose after resuscitation from out of-hospital CA and were cooled to 33°C for 12 to 24 hours (The Hypothermia After Cardiac Arrest study group 2002, Bernard et al 2002). These studies and the mode of action of hypothermia are reviewed in sections 2.5 and 2.9.

Several human studies have reported a strong association between high blood glucose level after resuscitation from CA and poor outcome (Longstreth et al 1983a, Longstreth and Inui 1984, Mullner et al 1997, Skrifvars et al 2003, Langhelle et al 2003). Keeping the blood glucose level between 4.4 and 6.1 mmol/L with insulin has reduced the hospital mortality rates in critically ill adults treated in surgical ICUs (van den Berghe et al 2001), but not in patients treated in medical ICUs (van den Berghe et al 2006). The optimal blood glucose level in patients resuscitated from CA has not yet been determined. The treatment recommendation is to monitor blood glucose frequently after CA, treat hyperglycemia with insulin, and avoid hypoglycemia (International consensus on cardiopulmonary resuscitation 2005).

Seizures after CA increase the oxygen requirements of the brain and can also cause cardiac arrhythmias and respiratory arrest; they should thus be treated effectively (International consensus on cardiopulmonary resuscitation 2005). No studies examine the possible benefits of prophylactic use of anticonvulsant drugs after CA.
2.5 Mode of action of hypothermia

Temperature plays a crucial role in determining degree of ischemic injury (Busto et al 1987, Minamisawa et al 1990, Ginsberg et al 1992). Hypothermia influences a variety of pathophysiological mechanisms during cerebral ischemia. Hypothermia’s protective effect is explained by a synergism of beneficial effects on multiple deleterious cascades that would lead to delayed neuronal death (Kataoka and Yanase 1998, Polderman 2004a).


Lowered temperatures reduce metabolic rate and oxygen consumption (Bigelow et al 1950b, Rosamoff and Holaday 1954, Chopp et al 1989). Cerebral metabolism is reduced by 5 to 7% for each degree C during induction of hypothermia (Milde 1992). Hypothermia prevents cell injury from leading to apoptosis, an effect that appears to be mediated by inhibition of caspase activation and prevention of mitochondrial dysfunction (Xu et al 2002, Ning et al 2002).

Hypothermia is also known to maintain the integrity of the blood-brain barrier after ischemic damage (Dietrich et al 1990, Karibe et al 1994, Preston and Webster 2004) and to prevent increased vascular permeability (Jurkovich et al 1988, Fischer et al 1999). Hypothermia thus appears to possess a membrane- and blood-brain barrier-stabilizing effect that may lead to reduced edema. At least in stroke patients, static cerebral autoregulation appears intact during hypothermia of 33°C with the use of alpha-stat for pH maintenance (Georgiadis et al 2002a).

2.6 Physiological and pathophysiological effects of mild to moderate hypothermia

Induction of hypothermia causes a number of physiological changes. Its physiological and pathophysiological effects depend largely on degree of hypothermia. Usually the levels are divided into mild (33–36°C), moderate (28–32°C), deep (<28°C), profound (<15°C) and ultraprofound (<5°C) hypothermia. In this review, the focus is on the effects of mild or moderate hypothermia.

Potential and frequent side-effects of mild to moderate hypothermia
include coagulopathy and impaired coagulation cascade, electrolyte disorders, increased diuresis, insulin resistance, and changes in drug effects and drug metabolism. Myocardial ischemia, infections, and severe coagulation disorders may also occur (Polderman 2004b).

The coagulopathy encountered with hypothermia is related to an increase in bleeding time, thrombocytopenia, and thrombocytopenia (Valeri et al 1987, Polderman 2004b). The prothrombin and partial thromboplastin times are prolonged by hypothermia, if the analyses are performed at the patient's actual core temperature (Rohrer and Natale 1992). However, risk for significant bleeding complications like intracerebral bleeding is very low.

Common electrolyte disorders include loss of K, Mg, Pi, and Ca, and hypothermia-induced diuresis may enhance this phenomenon. Hypothermia produces hypokalemia by a shift of potassium from the extracellular to intracellular or extravascular spaces. Aggressive potassium replacement therapy can lead to hyperkalemia on rewarming (Koht et al 1983). Moreover, serum glucose levels may increase, due to decreased insulin sensitivity and secretion, and serum lactate levels also tend to rise. An at least mild increase in serum amylase levels is common, but manifest pancreatitis is rare (Polderman 2004b).

Hypothermia inhibits various inflammatory responses and can impair immune function. Some studies involving stroke or traumatic brain-injury patients have reported a higher incidence of pneumonia when therapeutic hypothermia has been used for over 48 hours (Shiozaki et al 2001, Schwab et al 2001). Mild hypothermia lasting for 24 hours or less does not appear to raise the risk of infection (Marion et al 1997, Bernard et al 2002, The Hypothermia After Cardiac Arrest study group 2002).

Duration of action of the muscle relaxants vecuronium and pancuronium is prolonged by hypothermia (Sessler 2001), and hypothermia raises the plasma concentrations of propofol and fentanyl, when compared to normothermia (Sessler 2001). The plasma concentration of midazolam is also increased below the core temperature of 35°C (Fukuoka et al 2004).

Mild hypothermia is associated with bradycardia caused by decreased atrioventricular conduction velocity (Mattu et al 2002). With progressing hypothermia, junctional rhythm and atrial dysmrrhythrias may both occur. A significant risk for severe ventricular arrhythmias occurs only at temperatures below 28 to 30°C, but atrial fibrillation may occur at temperatures below 33°C (Okada 1984, Mattu et al 2002, Polderman 2004b). Cardiac output is reduced by hypothermia, and electrocardiography (ECG) changes are common in moderate hypothermia. Increased PR-interval, widening of the QRS-complex and increased QT-interval may occur at temperatures below 33°C (Polderman 2004b). The J-wave, also called the Osborn wave, is a positive deflection in the terminal portion of the QRS complex. It usually occurs in patients with a core temperature below 32°C, and can be detected in 80% of patients below a temperature of 30°C (Mattu
et al 2002, Nolan and Soar 2005). The ECG changes in a hypothermic patient can also mimic those of acute coronary ischemia or infarction, but this usually occurs at core temperatures below 32°C (Mattu et al 2002).

2.7 Cooling methods

Several cooling methods have been reported. These include ice bags, blankets containing circulating coolant or cold air, a helmet or cooling cap with chemical cooling capacities, drugs, cold carotid artery infusion, ice water nasal lavage, cold peritoneal lavage, cardiopulmonary bypass, and endovascular cooling with a catheter (Sterz et al 2003). Cold (4°C) lactated Ringer solution infused at 30 mL/kg over 30 minutes after resuscitation from out-of-hospital CA has been a safe and effective technique for inducing mild hypothermia (Bernard et al 2003, Kim et al 2005). This technique has been feasible and effective also in prehospital settings (Virkkunen et al 2004), and has also been studied in combination with endovascular cooling or with ice-water cooling blankets (Kliegel et al 2005, Polderman et al 2005). In an animal study, extracorporeal venovenous cooling has been reported as a promising method to rapidly induce therapeutic mild hypothermia (Holzer et al 2005a).

2.8 Core temperature measurement

When induction of hypothermia is planned, core temperature should be monitored accurately and continuously. Temperature can be monitored from blood, nasopharynx, esophagus, bladder, or rectum. During steady state and normal circulation the temperature gradient among brain, bladder, and rectal temperatures is minimal (Eshel and Safar 1999). However, during a rapid temperature change, nasopharyngeal, esophageal, and pulmonary artery temperatures correspond to brain temperature with smaller mean differences than do those of the tympanic membrane, bladder, or rectum (Eshel and Safar 1999, Stone et al 1995). Bladder temperature tends to lag behind core temperatures particularly during rapid cooling and rewarming (Crowder et al 1996). During mild hypothermia the jugular bulb temperature is similar to pulmonary artery and esophageal temperatures (Crowder et al 1996) and reflects closely the brain surface temperature (Ao et al 2000). Tympanic temperature monitoring may be used in pre-hospital settings, but it is less accurate. Usually after arrival at the hospital it is most convenient to monitor bladder temperature, as it closely reflects core temperature during maintenance of hypothermia, but at least during the cooling phase a second method of temperature measurement should also be used.
2.9 Clinical studies with induced hypothermia

2.9.1 Cardiac arrest

The use of therapeutic hypothermia for CA was reported as early as 1958, when Williams and Spencer published four cases of in-hospital CA successfully resuscitated and treated with hypothermia of 30 to 33°C for 24 to 72 hours. Two of the patients were children and two adults. All survived with good neurological outcome, although one adult patient experienced a visual defect after the incident (Williams and Spencer 1958). These four patients were also included in the study of Benson et al, published in 1959, presenting the outcome of 12 patients treated with therapeutic hypothermia of 30 to 32°C for 24 hours to 8 days after in-hospital CA and comparing theirs to the outcome of normothermia-treated controls. The outcome was good in half of the 12 hypothermic patients, but only in one of the 7 normothermic controls (Benson et al 1959).

Bernard et al published in 1997 a report of prospective hypothermia after CA, in which 22 patients were cooled to 33°C for 12 hours with ice-packs. Their outcome was compared to that of historical control subjects. Only 5 controls survived, but 12 hypothermia-treated patients, and the neurological outcome of the latter survivors was also better (Bernard et al 1997). Yanagawa et al reported in 1998 the outcome of 13 adult patients resuscitated from CA and treated with hypothermia of 33 to 34°C for 48 hours, followed by a very slow rewarming period. Their outcome was compared to that of 15 historical controls: Seven (54%) patients survived, as compared to five (33%) controls, with full recovery in three patients and one control subject, but hypothermia treatment was associated with an increase in pneumonic complications (Yanagawa et al 1998). Later, Nagao et al combined hypothermia with emergency cardiopulmonary bypass and intra-aortic balloon pumping for patients without restoration of spontaneous circulation (ROSC) on arrival at the emergency department. Hypothermia of 34°C lasted for at least 48 hours for 23 patients after the cardiopulmonary bypass. At hospital discharge, 12 of them (52%) showed good neurological outcome (Nagao et al 2000). The pilot trial of the HACA study comprised 27 patients treated with hypothermia of 33°C for 24 hours after CA. At 6 months 14 (52%) had achieved good outcome (Zeiner et al 2000). The feasibility trial of Felberg et al reported the outcome of nine CA patients treated with 24-hour hypothermia of 33°C, induced with cooling blankets. Outcome was favorable in 3 (33%) patients (Felberg et al 2001). A summary of these studies is presented in Figure 1.
Two independent prospective randomized clinical trials on hypothermia after CA appeared in 2002. In the Australian trial of Bernard et al, 77 patients with ROSC after VF or pulseless VT CA were randomly assigned to hypothermia (N=43) or normothermia (N=34). The hypothermia of 33°C was accomplished with ice-packs and was continued for 12 hours. The outcome was considered good if the patient was discharged home or to a rehabilitation facility, and poor, if the patient died or was discharged to a long-term care facility. In the hypothermia group, 21 (49%) patients achieved good outcome, compared to 9 (26%) patients in the normothermia group (p=0.046). After adjustments for baseline differences, the odds ratio (OR) for good outcome with hypothermia was 5.25 (95% confidence interval (CI) 1.47-18.76). No differences emerged in the frequency of adverse events (Bernard et al 2002).

The European multicenter study included 275 adult patients from nine centers in five European countries. These patients had been resuscitated from VF or non-perfusing VT CA, and were comatose on admission to emergency departments. Patients were randomly allocated to treatment with hypothermia (N=137) or with normothermia (N=138). Patients randomized to hypothermia were cooled to 33°C for 24 hours with an external air-cooling device. The primary outcome measure was favorable neurological outcome assessed at 6 months after CA by the Pittsburgh
Outcome Scale. A good outcome was achieved by 75 (55%) hypothermia patients and 54 (39%) normothermia patients (p=0.009). In the hypothermia group, 56 (41%) patients had died, as compared to 76 (55%) (p=0.02) (The Hypothermia After Cardiac Arrest study group 2002). Detailed results of this study are presented in the Results section. Figure 2 presents the neurological outcome in randomized clinical trials.

![Figure 2: Favorable neurological outcome in randomized clinical trials of therapeutic hypothermia after cardiac arrest, with number of subjects in each study.](image)

Large randomized studies addressing therapeutic hypothermia after out-of-hospital CA with initial rhythms other than VF have not appeared thus far. Polderman et al have reported in an abstract the outcome of 68 patients resuscitated from witnessed out-of-hospital CA with asystole or pulseless electrical activity (PEA) as their initial rhythm and treated with hypothermia of 32 to 33°C for 24 hours. At 6 months, the outcome was favorable in 32% of the hypothermia-treated patients, as compared to 16% of the historical controls (Polderman et al 2003, abstract). In a feasibility study investigating mild hypothermia induced by a helmet device, Hachimi-Idrissi et al studied 30 patients resuscitated from out-of-hospital CA with asystole or PEA as their initial rhythm. Good outcome was observed in 2 of 16 patients randomized to hypothermia of 34°C for a maximum of 4 hours but in none of the 14 patients randomized to normothermia (Hachimi-Idrissi et al 2001). The HACA Registry has reported the outcome data of 197 CA patients resuscitated from asystole or PEA. The outcome was unfavorable in 81% of hypothermia-treated patients (N=124) and in 81% of normothermia-treated patients (N=73) (Arrich et al 2007).
any randomized trials reported on the use of hypothermia for patients successfully resuscitated from in-hospital CA.

A meta-analysis combining three randomized controlled trials (The Hypothermia after cardiac arrest study group 2002, Bernard et al 2002, Hachimi-Idrissi et al 2001), with a total of 385 adult patients resuscitated from witnessed CA and treated with hypothermia, showed the number-needed-to-treat (NNT) to allow one additional patient to be discharged from hospital with favorable neurological recovery to be six (95% CI 4–13); the NNT for being alive and with favorable neurological status at 6 months after CA was also six (95% CI 4–25) (Holzer et al 2005b).

A recently published retrospective cohort study of adult comatose patients resuscitated from VF or other rhythms, both after out-of-hospital and in-hospital arrests, and also patients with extra-cardiac cause for the CA, reported that endovascular cooling after resuscitation significantly reduces mortality and improves favorable neurological recovery in unselected CA survivors (Holzer et al 2006). The 30-day survival and neurological outcome of these patients were then compared to those of controls not treated with hypothermia: 67 of 97 patients (69%) in the endovascular-cooling group and 466 of 941 patients (50%) in the control group survived at least 30 days. OR for survival in the cooling group was 1.96 (95% CI 1.19–3.23, p=0.008) after adjustment for baseline imbalances. In the endovascular cooling-group, 51 of 97 patients (53%) survived with favorable neurology as compared with 320 of 941 (34%) in the control group with adjusted OR 2.56 (95%CI 1.57–4.17, p<0.001).

The HACA Registry has published the data on 462 CA patients treated with hypothermia (Arrich et al 2007). The majority of patients (68%) were resuscitated from VF CA, but the population also included patients with the first cardiac rhythm of asystole (18%) or PEA (9%). Of these patients, 75% were cooled with an endovascular device, and 25% underwent other cooling methods. Of the total, 46% achieved a good outcome (Cerebral Performance Category (CPC) 1 or 2), compared to 32% of non-cooled CA patients also entered into this registry (N=123) (p<0.01), and 43% of hypothermia-treated and 68% of normothermia-treated patients died during their hospital stay (p<0.001).

The recommendation of the International Liaison Committee on Resuscitation from October 2002 states that unconscious adult patients with spontaneous circulation after out-of-hospital CA should be cooled to 32 to 34°C for 12 to 24 hours when the initial rhythm is VF, and that such cooling may also be beneficial for other rhythms or in-hospital CA (Nolan et al 2003). The recent guidelines of the American Heart Association in collaboration with the International Liaison Committee of Resuscitation give a similar recommendation (International consensus on cardiopulmonary resuscitation 2005). The new update of Utstein templates for resuscitation registries recommend that whether hypothermia was
induced in the postresuscitation phase should be included in the report as a core element (Jacobs et al 2004). In Europe, therapeutic hypothermia after CA has been widely adopted, and registries have been founded to follow up the use of this treatment and patient outcome (HACA-Registry, Northern Hypothermia network). Internationally, the situation varies. In a recent practice survey addressing the use of hypothermia after CA in the USA, 87% of the responders practicing emergency medicine, critical care, or cardiology had not used it (Abella et al 2005). In a similar survey a year later, the percentage of non-users was 74% in the USA, 69% in Great Britain, and 39% in Finland (Merchant et al 2006).

2.9.2 Therapeutic hypothermia for traumatic brain injury

Several clinical trials have assessed the effect of therapeutic hypothermia in patients with severe head injury (Clifton et al 1993, Shiozaki et al 1993, Hayashi et al 1994, Metz et al 1996, Marion et al 1997, Tateishi et al 1998, Nakamura et al 1998, Clifton et al 2001, Polderman et al 2002). Some of these studies have made special attempts to control intracranial hypertension in the severely head-injured patients (Shiozaki et al 1993, Hayashi et al 1994, Tateishi et al 1998, Polderman et al 2002). The initial results appeared very promising, but the randomized, controlled, prospective multicenter trial of Clifton et al comprising 392 patients showed no improvement in the outcome in hypothermia-treated patients with severe brain injury (Clifton et al 2001). It has later been suggested that the findings in this trial might have been influenced by the fact that the side-effects of artificial cooling had not been sufficiently taken into account.

Polderman et al studied therapeutic hypothermia in 136 patients with traumatic brain injury and with intracranial pressure (ICP) above 20 mmHg despite strictly standardized therapy for elevated ICP. Those who did not respond to barbiturate coma were treated with hypothermia of 32 to 34°C for at least 24 hours. When compared to a control group of patients who had responded to the barbiturate coma, the hypothermia-treated patients achieved a good neurological outcome significantly more often, and the mortality was also lower in the hypothermia-treated group (Polderman 2002). In the largest published study thus far, Zhi et al reported on the outcome of 396 patients randomly assigned to mild hypothermia or normothermia after severe head injury. In the hypothermia group, the proportion of patients with good neurological outcome was significantly higher (39% vs. 20%) and the mortality was lower (26% vs. 36%) than for the normothermia group (Zhi 2003). Jiang et al compared the effect of long-term hypothermia (5 days) versus short-term hypothermia (2 days) on the outcome of 215 patients with severe traumatic brain injury. In their study, the proportion of patients with favorable neurological outcome at 6 months follow-up was significantly higher in the group treated with long-term mild hypothermia (33–35°C), as compared to short-term hypothermia (44% vs. 23).
The authors suggest that early rewarming in patients with severe traumatic brain injury may lead to rebound intracranial hypertension and poor long-term outcome (Jiang et al 2006). Therapeutic hypothermia after traumatic brain injury has also been studied in children, and it has been assessed as likely to be a safe intervention, but its effect on functional outcome in children has not been determined (Adelson et al 2005). The possible benefit of mild to moderate hypothermia after severe traumatic brain injury still remains controversial. Two meta-analyses suggest that this intervention should not be used outside of controlled trials (McIntyre et al 2003, Alderson et al 2004).

2.9.3 Therapeutic hypothermia after ischemic stroke
In clinical settings, a rise in body temperature is highly correlated with stroke morbidity and mortality (Reith et al 1996, Hajat et al 2000). The experimental studies of focal ischemia have indicated that hypothermia is more effective when started early and maintained for relatively long periods (Maier et al 1998). Most clinical studies investigating the efficacy of therapeutic hypothermia have studied patients with malignant median cerebral artery (MCA) infarction.

In the first published study reporting the outcome of 25 hypothermia-treated patients with severe MCA infarction, mortality was 44%, but in the survivors the outcome was favorable (Schwab et al 1998). In a prospective multicenter study with 50 similar patients, mortality was 38%, and 3 months after the stroke the mean modified Rankin scale score was 2.9 (Schwab et al 2001). In both these studies an uncontrollable ICP increase during the rewarming period occurred in some patients. However, a study comparing the outcome of patients with severe acute MCA infarction treated with hemicraniectomy or moderate hypothermia found that hemicraniectomy resulted in lower mortality (12% vs. 47%) and lower complication rates (Georgiadis et al 2002b). In a randomized feasibility trial for endovascular cooling, a hypothermia of 33°C for 24 hours seemed to be well tolerated in patients with acute ischemic stroke, but the 30-day clinical outcomes and changes in infarct volumes in magnetic resonance imaging (MRI) did not differ between the hypothermia-treated and control patients. In that trial, 70% of the patients also received thrombolysis (De Georgia et al 2004).

Thus far, only three studies have investigated the early use of hypothermia in patients with ischemic stroke. The Copenhagen study examined the feasibility of early mild hypothermia in awake patients: For 6 hours, 17 patients were cooled to 35.5°C by external cooling. No adverse events were associated with the cooling, but the outcome of the hypothermia-treated patients was no better than that of the controls (Kammersgaard et al 2000). In the study of Krieger et al, early therapeutic hypothermia was combined with thrombolysis. They reported that this treatment was feasible in ten patients with severe acute ischemic stroke (Krieger et al 2001). Guluma
et al studied ten patients with acute ischemic stroke treated with both thrombolysis and hypothermia of 33 to 34°C for 24 hours. They used endovascular cooling in awake, non-intubated patients and reported that this method was feasible (Guluma et al 2006). The results of studies testing hypothermia as a treatment for acute ischemic stroke remain preliminary. Important questions remain regarding patient selection, optimal timing, duration and depth of cooling, and methods to minimize hypothermia-related complications (Schwab 2005). Studies are also needed to investigate the safety and effect of hypothermia in combination with thrombolysis or other neuroprotective methods (Hemmen and Lyden 2007).

2.9.4 Therapeutic hypothermia for HIE in the newborn infant
Perinatal hypoxic-ischemic brain injury remains an important cause of neurological disability. The current treatment for infants with HIE is supportive, but several studies have examined the safety and efficacy of induced hypothermia of 33 to 34°C as treatment after cerebral hypoxia-ischemia in term newborn infants. These trials have used both whole-body cooling and selective head cooling.

A randomized pilot-study comprising 32 severely affected neonates treated with hypothermia of 33°C for 48 hours and compared to 33 control patients reported poor outcome in 52% of those hypothermia-treated and in 84% of normothermia-treated patients (Eicher et al 2005). A randomized controlled trial of Gluckman et al suggested that delayed head cooling could improve outcome in infants with less severe amplitude-integrated electroencephalography (aEEG) changes. They studied 234 term infants with moderate to severe neonatal encephalopathy and abnormal aEEG. These infants were randomly assigned to either selective head cooling for 72 hours within 6 hours of birth, with rectal temperature maintained at 34 to 35°C, or to conventional care. Of the 118 infants allocated to conventional care 66% died or had severe disability, and 55% of the 116 infants assigned to head cooling died or had severe disability at 18 months. Predefined subgroup analysis suggested that head cooling had no effect in infants with the most severe aEEG changes. No difference was noted in the frequency of clinically important complications (Gluckman et al 2005). A MRI study comprising 34 term infants with HIE reported that hypothermia of 33 to 34°C for 48 to 72 hours resulted in a decrease in basal ganglia and thalamic lesions when compared to the MRI findings for 52 noncooled infants. In this study, the decrease was also significant in infants with a moderate aEEG finding, but not in those with severe aEEG findings (Rutherford et al 2005).

The study of Shankaran et al comprised 208 infants with moderate or severe encephalopathy, 102 of whom were assigned to whole-body cooling to an esophageal temperature of 33.5°C for 72 hours; 106 made up the
control group. Adverse events were similar in the two groups. Death or moderate or severe disability occurred in 44% in the hypothermia group and 62% in the control group, evaluated at 18 to 22 months. There was no increase in major disability among survivors (Shankaran et al 2005). Studies are needed to identify shortly after birth those infants who will benefit from hypothermic treatment, and to gather information about the long-term outcome of these infants (Thoresen and Whitelaw 2005).

2.10 Prediction of outcome after cardiac arrest

Most patients resuscitated from CA are initially comatose (Longstreth et al 1983b). Early prediction of neurological outcome in patients resuscitated from CA is a major ethical, medical, and socioeconomical challenge. To avoid a falsely pessimistic prognosis, the prognostic tests used in critical care are usually required to have high specificity and a narrow CI for poor outcome, with less emphasis on sensitivity. A false prognosis of poor outcome can lead to early withdrawal of care and carries thus the risk of a self-fulfilling prophecy. On the other hand, a falsely optimistic prediction may lead to unnecessary prolongation of intensive care therapy and might prevent admission of other patients who could benefit more.

2.10.1 Clinical status

The times from collapse to the start of basic and advanced life support and especially to defibrillation correlate with survival rate (Weaver et al 1986, Roine 1993a, Rogove et al 1995). The prognosis worsens with increasing duration of coma. Generally the awakening takes place within 3 days after CPR (Longstreth et al 1983b, Levy et al 1985). No clinical findings on admission have been proven reliably to predict poor outcome. In a recent meta-analysis of Booth et al covering all 11 studies between the years 1979 and 2000 studies, addressing clinical signs in outcome prediction after CA for a total of 1914 comatose survivors of CA, the conclusion was that prognostic assessment on clinical grounds is impossible before 24 hours have elapsed and for motor signs before 72 hours (Booth et al 2004). Patients sedated or anesthetized during the clinical examination were not included in the analysis. The most useful signs predicting poor outcome were absent corneal reflexes, absent pupillary reflexes, and absent motor response, all at 24 hours, and absent withdrawal from pain at 72 hours after CA (Booth et al 2004). However, heavy sedation and opiate analgesia are now used much more frequently and in higher doses than a few decades ago, and this may confound the clinical status. Generalized myoclonic status has been reported to be a terminal finding after CA and to be incompatible with recovery (Wijdicks et al 1994, Hui et al 2005), but early myoclonic status is not necessarily an agonal event (Morris et al 1998).
2.10.2 Serum biochemical markers

Neuron-specific enolase (NSE) is the neuronal form of the intracytoplasmic glycolytic enzyme enolase. NSE, located in neurons and in neuroectodermal cells (Schmechel et al 1978a, 1978b), is a dimeric enzyme composed of two γ subunits, with a molecular weight of 78 kD and a biologic half-life of approximately 24 hours. Evidence of neuronal damage and impairment of blood-brain-barrier integrity is the release of NSE into the cerebrospinal fluid (CSF) and eventually into the blood. Increased levels of CSF and serum NSE occur after ischemic stroke, intracerebral hemorrhage, brain injury, and CA (Cunningham et al 1991, Barone et al 1993, Skogseid et al 1992, Persson et al 1987, Roine et al 1989, Kärkelä et al 1993). Several studies have found high levels of serum NSE to be associated with poor outcome in patients resuscitated from CA (Stelzl et al 1995, Martens 1996, Fogel et al 1997, Martens et al 1998, Schoerkhuber et al 1999, Rosen et al 2001, Meynaar et al 2003, Rech et al 2006, Reisinger et al 2007). There exist some confounding factors in the accurate determination of NSE. Hemolysis can result in falsely increased serum NSE values, as NSE can be found in red blood cells and platelets, as well as in neuroectodermal tumors. NSE is at least partly metabolized by the kidneys, and patients with renal failure show increased levels of serum NSE (Cases et al 1991, Nomura et al 1998).

Proposed NSE cut-off levels for poor neurological outcome with a specificity of 95 to 100% have differed, ranging from 25 to 80 μg/L. Several reasons for these discrepancies have been identified. First, sample size has been relatively small in most of the studies. Second, the definition of poor neurological outcome has differed between studies: Some studies have classified CPC 3 together with CPC 4 and 5 as poor neurological outcome, but other studies had poor neurological outcome only as CPC 4 or 5. Third, laboratory assays for determination of serum NSE have differed between investigations. The recently published recommendations of the American Academy of Neurology state that serum NSE > 33 μg/L at days 1 to 3 after CPR accurately predicts poor outcome (Wijdicks et al 2006). This has been criticized by Reisinger et al, who in their study population of 177 CA patients reported nine patients with grade CPC 1 or 2 recovery and serum NSE levels exceeding 33 μg/L (Reisinger et al 2007). Data on NSE levels in hypothermia-treated CA patients is still very limited.

The S-100B protein is an acidic Ca\textsuperscript{2+}-binding protein with a molecular weight of approximately 21 kD and biologic half-life of 0.5 hours (Jönsson et al 2000). It has two subtypes, αβ-heterodimer and ββ-homodimer. The αβ form occurs in astroglial cells; the ββ form occurs predominantly in astroglial and Schwann cells but has also been demonstrated in tumors such as melanoma, schwannoma, and highly differentiated neuroblastoma, and in melanocytes, adipocytes, and chondrocytes (Kligman and Hilt 1988, Zimmer et al 1995). Increased serum levels of protein S-100B appear after
traumatic brain injury, stroke, CA, and cardiopulmonary surgery (Raabe et al 1998, Elting et al 2000, Missler et al 1997, Jömsson et al 2001, Martens et al 1998). High levels of serum S-100B on admission or at 12, 24, 48, or 72 hours after CA correlate with unfavorable neurological outcome (Martens et al 1998, Rosen et al 1998, Rosen et al 2001, Böttiger et al 2001, Hachimi-Idrissi et al 2002, Mussack et al 2002). Hachimi-Idrissi et al have reported that serum S-100B levels decrease significantly between admission and 24 hours after CA in patients treated with mild hypothermia (Hachimi-Idrissi et al 2005). Detection of the β-subunit of S-100B has been considered to be brain-specific. However, Anderson and his colleagues demonstrated extracerebral sources of contamination in cardiac operations (Anderson et al 2001), and this was later confirmed by Snyder-Ramos et al (Snyder-Ramos et al 2004). Experimental studies have suggested that local extracranial ischemia and reperfusion per se may cause an increase in S-100B (Pelinka et al 2004). No certainty thus exists that all of the S-100B detected in the peripheral blood of CA patients originates from the brain.

The anaerobic glycolysis in anoxic injury leads to overproduction of lactate. The high levels of arterial lactate concentration on admission after out-of-hospital VF CA are associated with severe neurological impairment. This parameter is of poor prognostic value, however, for individual estimation of the severity of subsequent neurological impairment (Mullner et al 1997). Serial lactate determinations are more useful in outcome prediction. Lactate levels exceeding 2 mmol/L at 48 hours after CA have predicted mortality with a specificity of 86% and poor neurologic outcome with a specificity of 87%. Sensitivity for both end-points was 31% (Kliegel et al 2004). As hypothermia frequently induces an increase in serum lactate levels (Polderman 2004b), the prognostic value of serum lactate levels should thus be validated in further studies in hypothermia-treated CA patients.

Brain natriuretic peptide (BNP) is a cardiac neurohormone of the natriuretic peptide system, predominantly secreted by the cardiac ventricles (Mukoyama et al 1991). Two recent studies found that the BNP level measured from serum on arrival in the emergency room predicted neurological outcome and survival after CA (Sodeck et al 2007, Nagao et al 2007). Sodeck et al measured BNP in 155 comatose CA survivors at hospital admission. Their outcome was assessed 6 months after CA. The median level of BNP was 30 pg/mL in patients with good neurological outcome and 87 pg/mL in patients with poor outcome (p=0.006). In multivariable analysis, levels of BNP over 230 pg/mL predicted unfavorable neurological outcome (OR 2.25, 95% CI 1.05–8.81) and failure to survive for 6 months (OR 4.7, 95% CI 1.27–17.35) (Sodeck et al 2007). Nagao et al studied 109 comatose patients resuscitated from out-of-hospital VF or VT CA due to cardiac causes and treated with mild therapeutic hypothermia of 34°C for 2 days. Their outcome was assessed at hospital discharge. In this study, a BNP level exceeding 80 pg/mL
was an independent predictor of unfavorable neurological outcome. A BNP level over 300 pg/mL had a negative predictive value of 100% for favorable neurological outcome (Nagao et al 2007). Measurement of serum BNP thus appears to be a very promising new prognostic indicator, but further studies are still needed to confirm these findings and to establish a defined cut-off value for clinical use.

2.10.3 Evoked potentials

Somatosensory evoked potentials (SEPs) provide information about the brain stem sensory pathways, thalamo-cortical projections, and primary somatosensory cortex. The short-latency median nerve SEPs accurately predict permanent coma after CA (Zandbergen et al 1998, Robinson et al 2003). Short-latency SEP recording is a non-invasive, reproducible technique requiring no patient cooperation that can be easily performed bedside in intensive care. Short-latency SEPs are also quite resistant to anesthetic agents (McPherson et al 1986). The cortical N20 response is the first cortical response, occurring approximately 20 ms after stimulation to the median nerve at the wrist. A bilaterally absent early cortical N20 response predicts permanent coma with a specificity of 100% (95% CI 99-100%), and thus the median nerve SEP can be regarded as the method of choice for predicting outcome after CA (Zandbergen et al 1998, Robinson et al 2003). Significant improvement in SEP has been reported within 24 hours after ROSC (Gendo et al 2001); allowing a period of at least 24 hours after CA is best for a reliable prognosis based on SEP. Normal cortical SEP responses do not, however, guarantee awakening from coma.

Long-latency SEPs (N70 response) have been suggested to indicate favorable outcome (Madl et al 1993), but this finding could not be confirmed in a recent study (Zandbergen et al 2006b). Madl et al have also reported the N70 long-latency SEP to be more accurate in predicting individual outcome than was a panel of three experienced emergency physicians reviewing clinical data 24 hours after CA (Madl et al 2000). Recording of long-latency SEPs is more demanding than for short-latency SEPs, since long-latency SEPs are often less reproducible and more prone to artifacts, which may be an issue especially in the ICU environment.

Brain stem auditory evoked potentials (BAEPs) evaluate the functional state of brain stem auditory pathways in the pons, the lower part of the mesencephalon, up to the inferior colliculi. BAEPs have been used as a screening test for poor prognosis in comatose patients (Attia and Cook 1998). Measurement of middle latency auditory evoked potentials has been useful in monitoring neuronal function at the level of the primary auditory cortex. Bilateral abolition of cortical middle latency auditory evoked potentials has accurately predicted permanent coma after CA (Logi et al 2003, Fischer et al 2006). BAEPs are also quite resistant to anesthetic agents. Fentanyl at doses
up to 50 μg/kg i.v. had no significant effect on absolute or interpeak latencies of wave I, III, or V evoked potentials (Samra 1984).

Event-related potentials have also been studied in comatose patients. The presence of auditory evoked P300 potential may predict awakening from non-traumatic coma (Gott et al 1991, De Giorgio et al 1993). In patients remaining comatose after CA, the presence of mismatch negativity (MMN), the earliest component of event-related potentials, predicts a very high probability of awakening (Fischer et al 2006). The absence of P300 event-related potential or MMN does not, however, preclude awakening, as these responses cannot be demonstrated even from all healthy subjects.

Hypothermia raises all neuronal conduction velocities, and prolongs the SEP and BAEP latencies, and temperature also influences the amplitudes of SEP responses (Markand et al 1990b, Coles et al 1984, Zeitlhofer et al 1990, Porkkala et al 1997). In peripheral nerves, sensory nerve conduction velocity has been reported to decrease at a rate of about 2.0 m/s with each degree Celsius (Buchthal and Rosenfalck 1966). Mild to moderate hypothermia does not abolish cortical responses to SEPs (Markand et al 1990a). The cortical component N20 disappears only at a mean nasopharyngeal temperature of 20ºC under normal hemodynamic conditions (Coles et al 1984, Guerit et al 1994). Hypothermia causes an increase in BAEP interwave latencies (Markand et al 1990b, Stockard et al 1978, Markand et al 1987). BAEP components have been reported to be abolished at temperatures below 20ºC (Markand et al 1987).

Recently published guidelines state that median nerve SEPs measured 72 hours after CA predict a fatal outcome in patients with hypoxic-anoxic coma (International consensus on cardiopulmonary resuscitation 2005). If SEPs are recorded in patients with induced hypothermia, the intensity of the stimuli has to be sufficient to evoke an ipsilateral supraclavicular response in patients with clinical muscle relaxation. Due to the slowing of neural transmission with hypothermia (Benita and Conde 1972, Buchtal and Rosenfalck 1966), the N70 cut-off values determined on normothermic patients cannot be applied to hypothermic patients. Thus far no studies examining long-latency SEPs in hypothermic CA survivors have been published. Addition of NSE to short-latency SEPs increases predictability of neurological outcome (Meynaar et al 2003, Zandbergen et al 2006a). In a recently published study concerning 407 patients resuscitated from CA, Zandbergen et al concluded that poor outcome in postanoxic coma can be reliably predicted with bilaterally absent SEPs or serum NSE over 33 μg/L as early as 24 hours after CPR or both in a substantial number of patients (Zandbergen 2006a). Their study included only ten patients treated with hypothermia, but they concluded that the same criteria can also be used in patients treated with hypothermia.
2.10.4 Electroencephalography

The prognostic ability of electroencephalography (EEG) has also been studied in CA survivors. EEG sensitivity to drug effects and metabolic disturbances limits its prognostic usefulness. Only EEG with essentially complete generalized suppression after the first post-arrest day in the absence of sedative or anesthetizing drug effects is associated with invariably poor outcome. Neither suppression of EEG, periodic complexes, epileptiform activity, burst-suppression, nor alpha coma pattern precludes the possibility of neurologic recovery, although each usually indicates poor outcome (Young 2000). Serial EEGs may offer supplemental information about the evolution of the patient's status. Mild hypothermia produces small changes in the EEG (Kochs 1995).

Quantitative electroencephalography (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 (Geocadin et al 2000), and this method has also been studied in hypothermia-treated animals (Jia et al 2006). In humans, the prognostic value of continuous aEEG has been studied in CA patients treated with hypothermia. A continuous aEEG at normothermia, after 24 hours of induced hypothermia (mean 37 hours after CA) predicted recovery of consciousness, whereas flat, suppression-burst, or status epilepticus aEEG patterns indicated permanent coma (Rundgren et al 2006).

2.10.5 Neuroradiological imaging

In the acute stage, conventional MRI or computerized tomography (CT) may be useful for differential diagnostic purposes. In HIE, later neuroradiological imaging may reveal bilateral watershed infarcts, laminar cortical necrosis, or cerebellar, white matter, or basal ganglia lesions. Neuroradiological imaging findings seem to have limited prognostic value, with the exception of absent intracranial circulation or increased ICP. A normal conventional MRI or CT does not exclude the diagnosis of HIE (Roine et al 1993c). Fluid-attenuated inversion recovery and diffusion-weighted imaging may help detect extensive ischemic damage in comatose survivors of CA (Arbelaez et al 1999, Wijdicks et al 2001). The difficulty of performing MRI on critically ill patients often limits the use of this examination.

2.10.6 Limitations of outcome prediction methods

Currently the methods used in assessing neurological prognosis are targeted at prediction of poor outcome (persisting coma or death). Despite having all normal examination results, some survivors of CA never regain consciousness. Thus far, there are no methods to accurately predict good outcome in the early phase of treatment, although the presence of MMN or P300 event-related potentials suggest awakening from coma after CA.
Unfortunately, recording of these potentials is technically demanding in the ICU, and these methods are not widely available in the clinical ICU settings.

The use of therapeutic hypothermia seems to complicate early evaluation of outcome. The prediction methods developed on normothermic patients cannot be directly applied to patients treated with hypothermia without validation studies (Sunde et al 2006). The importance of clinical status is reduced by the use of therapeutic hypothermia. Induced hypothermia requires muscle relaxation, sedation, and mechanical ventilation, which may complicate clinical assessment. Muscle relaxation also masks myoclonic jerking and seizures. It has been suggested that EEG should be used in hypothermia-treated patients to detect possibly treatable epileptic activity (Hovland et al 2006). Hypothermia may also induce changes in drug metabolism and lengthen sedative drug effects (Sessler 1991). The possible effect of individual medications on a patient’s clinical status should always be carefully considered. Thus, the use of therapeutic hypothermia seems to postpone the first feasible prognostic evaluation.
3 AIMS OF THE STUDY

The objective of this study was to evaluate the effect of therapeutic hypothermia on the outcome of patients resuscitated from out-of-hospital CA and to evaluate the effects of therapeutic hypothermia on outcome prediction, cardiac arrhythmias, and neurological outcome.

The specific aims of this study were to answer the following questions:

Does induced hypothermia of 33°C after out-of-hospital VF CA improve neurological outcome and survival? (Study I)

What is the effect of therapeutic hypothermia on the release of serum markers of ischemic injury, NSE and S-100B, and what is the predictive value of these serum markers in hypothermia-treated CA patients? (Study II)

What is the effect of hypothermia of 33°C on SEP and BAEP? Is the predictive value of absent N20 cortical responses of SEP preserved in patients treated with hypothermia, and does combining BAEPs with SEPs result in improved outcome prediction? (Study III)

What are the cardiac effects of mild therapeutic hypothermia of 33°C in CA patients, especially the effect on cardiac arrhythmias and on heart rate variability (HRV)? Is HRV of predictive value in these patients? (Study IV)

Does the cognitive outcome of hypothermia-treated CA patients differ from that of those treated with traditional normothermia? Do the neurophysiological measurements Q-EEG and auditory evoked P300 event-related potential detect any differences between these treatment groups 3 months after CA? (Study V)
4 SUBJECTS AND METHODS

4.1 Study design

The HACA study was designed as a randomized, controlled prospective multicenter trial with blinded assessment of the outcome. The primary end-point of this trial was a favorable neurological outcome within 6 months after CA. Secondary end-points were mortality within 6 months and the rate of complications within 7 days.

Nine centers from five European countries participated in the HACA trial. Participating hospitals were Vienna University Hospital and Rudolfstiftung Hospital in Vienna, Austria; Helsinki University Hospital in Finland; Hospital Sint Jan in Bruges and Vrije Universiteit Hospital in Brussels, Belgium; Evangelisches Waldkrankenhaus Hospital and Rheinischen Friedrich-Wilhelms University Hospital in Bonn, Germany; and Niguarda Ca’ Granda Hospital in Milan and Ospedale di Careggi in Florence, Italy.

The substudies comprising Studies II to V of this thesis were performed on patients enrolled in the HACA trial in Helsinki.

4.2 Ethical aspects

The protocol and consent procedures were approved by the institutional review board of each participating center. In Helsinki the protocol and consent procedure of this study was approved by the ethics committee of Helsinki University Central Hospital in accordance with institutional guidelines. Because all patients were unconscious, a deferred consent was used for all. The patient's family was informed about the trial and had the possibility to withdraw the patient at any time from the study. Each patient, when he or she was able to receive this information, was informed about the trial both orally and in writing. The patient could then decide if he or she was willing to participate in the follow-up.
4.3 Inclusion and exclusion criteria

The criteria for inclusion were:
1. age of 18 to 75 years
2. a witnessed out-of-hospital cardiac arrest
3. ventricular fibrillation or nonperfusing ventricular tachycardia as the initial cardiac rhythm
4. a presumed cardiac origin of the arrest
5. an estimated interval of 5 to 15 minutes from the patient’s collapse to the first attempt at resuscitation by emergency medical personnel
6. an interval of less than 60 minutes from collapse to restoration of spontaneous circulation

The exclusion criteria were:
1. CA occurring after arrival of the first responding unit
2. patient responding to verbal command after ROSC and prior to randomization
3. CA due to intoxication or trauma
4. Glasgow Coma Scale over 8 on admission
5. a tympanic temperature below 30ºC on admission
6. evidence of hypotension (mean arterial pressure less than 60 mmHg) for more than 30 minutes after ROSC and before randomization
7. evidence of hypoxia (arterial O2 saturation less than 85%) for more than 15 minutes after ROSC and before randomization
8. a preceding terminal illness
9. a known pre-existing coagulopathy (use of warfarin or thrombolysis were not exclusion criteria)
10. known pregnancy
11. factors making participation in follow-up unlikely
12. enrollment in another study

4.4 Cardiac arrest, resuscitation, and acute care

During the present study, basic (BLS) and advanced cardiac life support (ACLS) were provided by the three-tiered Helsinki EMS in the Helsinki city area. Outside the city of Helsinki, the BLS was provided by the staff of regional fire brigade-based EMS, and ACLS by the emergency medical helicopter. All EMS units are equipped with semi-automatic defibrillators and are trained to intubate, insert intravenous (i.v.) catheters, and start medication. During the last 5 years, about 80 to 90 CA cases with VF or VT as the primary rhythm have occurred in the Helsinki city area every
year, and about 55 to 60% of these have been admitted to hospital (M. Kuisma and J. Boyd, personal communication, 2007). Before the trial began, the EMS physicians had been informed about the study protocol and selection criteria.

CA was defined as the absence of both palpable pulse and spontaneous respiration. ROSC was defined as the return of a palpable arterial pulse. All CA data were collected according to the Utstein style (Cummins et al 1991). The EMS units had been guided not to actively warm patients resuscitated from out-of-hospital CA.

Respiratory and hemodynamic functions were assessed and stabilized in the emergency room of Meilahti Hospital. All adult patients admitted to the emergency department of Helsinki University Hospital after resuscitation from out-of-hospital CA from March first 1997 to June 30, 2000 were screened for the trial. The investigator of this study was on call 24 hours a day, and was paged by the EMS units or by the emergency room physician. The investigator then arrived at the emergency room as soon as possible and assessed the patient's eligibility for the HACA trial. This assessment also included an initial neurological evaluation. Brain CT was performed, if the history or clinical findings suggested a cerebral cause for CA. Eligible patients were randomized to receive hypothermia or normothermia treatment by opening of the envelope next in order of consecutively numbered envelopes, each containing the treatment assignment. The sealed envelopes with pre-randomized treatment assignments had been delivered to Helsinki from Vienna by Professor Fritz Sterz, the principal investigator of the HACA study. Permission for the study was obtained from the patient's family, as soon as the family could be reached.

### 4.5 HACA ICU protocol

All patients received standard intensive care management and monitoring including mechanical ventilation, arterial and central venous catheters and a Foley catheter with a temperature sensor, and a pulmonary artery catheter as necessary.

Sedation and analgesia were accomplished by use of midazolam 0.125 mg/kg/hour and fentanyl 0.002 mg/kg/hour i.v., titrated for at least 32 hours. To prevent shivering, pancuronium 0.05 mg/kg/hour was initially used. The lowest dose that would permit muscle relaxation (train-of-four stimulation response 1/4) was used for a total of 32 hours. The degree of muscle relaxation was monitored with a neurostimulator hourly. All patients, also those assigned to normothermia, received pancuronium according to the HACA protocol. Mean arterial pressure was targeted at 80 mmHg. Arterial hypotension was treated primarily by infusing crystalloid fluids or hydroxyl ethyl starch as necessary, and inotropic agents were used.
if sufficient blood pressure control could not be achieved by fluid therapy alone. No glucose-containing solutions were given. Intravenous insulin infusion was administered if blood glucose concentration exceeded 10 mmol/L and was targeted at normoglycemia. Nutrition was not started until 48 hours after CA. The optimal direct head-up-position (30º) was maintained.

Patients randomized to normothermia were allowed to rewarm passively to normothermia (target temperature 37.5ºC) and were then kept normothermic by physical and anti-pyretic means. Those randomized to hypothermia treatment were actively cooled externally to a core temperature 33 ± 1ºC with a cooling device (Therakool® Kinetic Concepts Inc. United Kingdom, Wareham, UK). Their cooling device consists of a mattress and cover that delivers cold air over the entire body. To prevent pressure sores, the pressure in the mattress compartments changes constantly. If necessary, ice-packs were applied in the patient’s axilla and groin to enhance the cooling. Hypothermia of 33 ± 1ºC was maintained for 24 hours from the start of cooling and the patients were then allowed to rewarm over 12 hours. Administration of pancuronium was discontinued when core temperature exceeded 35ºC, but the sedoanalgesia was continued at the discretion of the treating physician.

Life-support was maintained for at least 3 days for all patients and at least 7 days in patients responding to pain in any manner. Data on serum NSE and S-100B levels were unavailable during the acute care, and the recordings of evoked potentials were analyzed retrospectively in a block. Results thus did not affect decisions whether to continue or withdraw intensive care. Withdrawal of intensive care meant withdrawal of inotropic i.v. medications but maintenance of airway and ventilator treatment.

### 4.6 Subjects

A total of 275 patients were enrolled in the HACA trial between March 1996 and July 2000, of whom 137 were assigned to hypothermia treatment and 138 to normothermia treatment. Of these, 90 patients were randomized in Vienna, 71 in Helsinki, 35 in Bruges, 25 in Brussels, 30 in Bonn, 12 in Milan, and 12 in Florence.

In Helsinki, the 71 patients were randomized to the HACA trial between March first 1997 and the end of June 2000. No one refused the trial. During this time, five eligible patients could not be randomized: three because the patient could not be admitted to the ICU, one because of lack of notification to the investigator, and one because of absence of the investigator. One patient randomized to normothermia treatment was later excluded from the HACA trial due to violations of inclusion criteria: the primary rhythm of this patient was asystole, as revealed by later analysis of the defibrillator
memory data, and the etiology of CA was subarachnoidal hemorrhage. This patient died without recovery of consciousness. The Helsinki study population thus comprised 70 CA patients, 36 of whom were randomized to hypothermia and 34 to normothermia treatment during the 3-year and 4-month study period.

All 70 patients are included in Studies I and IV. The subjects of Study II were the 68 patients alive at 24 hours after CA. Study III comprised the 60 consecutive patients alive at 24 hours after CA (patients 9–71), from whom the evoked potentials were recorded. Evoked potential recordings were not performed on the first eight patients, because we first focused on obtaining more experience of the cooling and rewarming process. The subjects of Study V were the 45 (of the 47) patients who were conscious and alive 3 months after CA and could attend the follow-up visit. Figure 3 presents the distribution of patients among Studies I to V.
Figure 3. Distribution and numbers of patients in Studies I to V
4.7 Measurements

4.7.1 Assessment of outcome

A standard neurological examination was performed daily during treatment in the ICU, on days 3, 7, and 14, at discharge from the hospital, and at 3 months after CA. The primary end-point was a favorable neurological outcome 6 months after CA as assessed by the Pittsburgh Outcome Scale (Jennet and Bond 1975, BRCT II study group 1991). This is a five-category scale of Cerebral Performance Categories (CPC) and Overall Performance Categories (OPC). The division into CPC and OPC allows the investigator to differentiate as to whether the patient's deficits on a functional level are caused by some cerebral factor or are related to other diseases. The definitions for CPC and OPC categories are presented in Table 1.

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<th>Table 1. Pittsburgh Outcome Scale</th>
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<td><strong>CPC 1</strong></td>
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<td><strong>CPC 3</strong></td>
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<td><strong>CPC 5</strong></td>
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<td><strong>OPC 1</strong></td>
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For statistical analyses, neurological outcome was dichotomized into good (CPC 1 and 2) or poor (CPC 3, 4, and 5). Good outcome implied independent function, whereas poor outcome implied loss of independence. The CPC class was determined by neurologist Olli Häppölä, MD, PhD, without knowledge of the treatment assignment. Assessment of outcome included an interview with the nearest relatives or with nursing staff for
institutionalized patients or with both. The following parameters were also recorded: the best achieved CPC within 6 months after ROSC, change in CPC from the pre-arrest level, recovery of consciousness (defined as the ability to obey verbal commands), and death.

4.7.2 Serum markers of neuronal injury
Blood samples for NSE and S-100B were collected from the arterial catheter at 24, 36, and 48 hours after ROSC. The blood was allowed to clot for 20 to 30 minutes at room temperature and then centrifuged and frozen to below -18°C. Samples which showed visible hemolysis were not analyzed. NSE was quantified with a time-resolved immunofluorometric assay (DELFIA®, Wallac, Turku, Finland), for which the detection limit is 1 μg/L. The upper reference limit is 12.5 μg/L (based on results from 402 apparently healthy adults, mean + 2 standard deviation (SD), manufacturer’s notice). S-100B was quantified with an automated immunoluminometric assay (LIAISON®, Sangtec Medical, Bromma, Sweden). This method detects the β-subunit of S-100B. The detection limit is 0.02 μg/L. The upper reference limit is 0.15 μg/L (mean + 2 SD, N=201, manufacturer’s notice).

4.7.3 Sensory and auditory evoked potentials
The SEPs and BAEPs were recorded 24 to 28 hours after CA by use of a four-channel electromyography/evoked potential device Medelec Sapphire® (Medelec Limited, Woking, Surrey, UK). For SEPs, square-wave pulses with a duration of 0.2 ms at a repetition rate of 3 pulses per second served as stimuli to the median nerve at the wrist. Stimulus intensity was 25–30 mA. Ag/AgCl surface electrodes were placed according to the International 10–20 System as follows: for the N9 peak on the ipsilateral Erb’s point (referenced to the contralateral Erb’s point), for the N13 peak on cervical spinous process C7 (referenced to the sternum), for P15 and N18 peaks on Fpz (referenced to the ipsilateral mastoideum) and for the N20 peak on the contralateral parietal (referenced to the ipsilateral parietal). Sweep time was 100 ms, amplifier sensitivity was 20 to 50 μV/div, display sensitivity was 1.0 to 2.5 μV/div, and bandwidth was 20 Hz to 1 kHz. Electrode impedances were maintained below 5 kOhm. Trials with excessive artifacts were rejected automatically. A mean of 610 trials (range 350–1050) were averaged. Recordings were performed twice for both right and left median nerve stimulation. The distance between stimulation site and Erb’s point was measured to calculate the nerve conduction velocity.

BAEPs were recorded by use of clicks of 105 dB intensity presented monaurally at a rate of 9 per second through earphones. A mask of 20 dB intensity was used in the contralateral ear. Sweep time was 10 ms, amplifier sensitivity was 5 to 10 μV/div, display sensitivity was 0.05 to 0.1 μV/div, and bandwidth was 100 Hz to 2 kHz. The Ag/AgCl surface electrodes were placed on the ipsilateral mastoideum and referenced to Fz. Responses of
2048 stimuli were averaged for an individual test, and the procedure was performed twice to both right and left ear stimulation.

The SEP and BEAP recordings were all analyzed retrospectively as a block. SEPs and BAEPs were analyzed by clinical neurophysiologist Tero Kovala, MD, PhD, who was blinded to the treatment and patient outcome. Means of left-sided and right-sided evoked potential stimulations were used for calculations. Amplitudes and latencies were calculated from cases with responses present.

4.7.4 Ambulatory ECG
Holter recordings
The 24-hour ambulatory ECG recordings were performed with a portable two-channel tape recorder (Medilog, Oxford Medical Ltd., Oxford, UK) three times during the first 2 weeks after CA. The first recording (referred to as 0–24 hour) was started, right after randomization, in the emergency room or in the ICU. The second recording was started immediately after the first recording (referred to as 24–48 hour). The third recording was done 14 days after CA. All patients were sedated and artificially ventilated during the first Holter recording. Pancuronium administration was discontinued during the second recording, but sedoanalgesia with midazolam and fentanyl was continued at decreasing doses. All patients remained in a supine head-up position (30º) during the first and second recordings. During the third recording, all patients were allowed normal physical activity. The tapes were analyzed in blinded fashion by two observers.

Definitions of arrhythmias
Supraventricular arrhythmias: The total number of supraventricular premature beats (SVPB) per hour was calculated from Holter recordings. A supraventricular run was defined as three or more consecutive premature beats at any rate. Atrial fibrillation was defined as irregular QRS complex interval and no detectable regular atrial activity.
Ventricular arrhythmias: The total number of premature ventricular beats (PVBs) per hour was measured. A ventricular run was classified as three or more consecutive PVBs at any rate. Three or more consecutive PVBs at a rate of > 120 beats/min was classified as VT.

4.7.5 Measurement of autonomic regulation of the heart
HRV evaluates beat-to-beat fluctuations in the sinus heart rate. These fluctuations are considered to arise from changes in autonomic inputs to the heart. HRV measured from a 24-hour ECG recording is thought to reflect the level of autonomic modulations to the heart rhythm. Depressed HRV, i.e., low values in the indexes measuring HRV, may be related to increased sympathetic excitation, depressed vagal activity, or reduced responsiveness of sinus nodal cells to neural modulation (Task Force for
HRV was assessed by time-domain and frequency-domain methods from the 24-hour Holter recordings. For HRV calculations, only normal sinus beat intervals were used. Ectopic or artifact periods were excluded and replaced by holding the previous coupling interval level through to the next valid coupling interval. Fast Fourier transformation was used to separate the R-R fluctuations to frequencies. The spectral bands used were 0.15 to 0.40 Hz (high frequency, HF), 0.04 to 0.15 Hz (low frequency, LF), and 0.01 to 0.40 Hz (total power). The spectral measures were computed as amplitudes, which are square roots of areas under the power spectrum, and are presented in ms. The areas represent signal variance within frequency bands, whereas the square root represents the standard deviation. The HF and LF components were determined from the entire 24-hour recording. LF power reflects sympathetic and parasympathetic modulations of heart rate, whereas HF power mainly reflects vagal modulation (Task Force for the European Society of Cardiology and North American Society of Pacing and Electrophysiology 1996). The following variables were used as the time-domain methods: the standard deviation of individual normal-to-normal (NN) intervals (SDNN), the standard deviation of the averaged NN intervals for all 5-minute periods of the 24-hour recording (SDANN), the root mean square of successive NN differences (rMSSD), and the relative number of NN intervals differing by more than 50 ms from the immediately preceding NN interval (pNN50). Both SDNN and SDANN reflect a mixture of sympathetic and parasympathetic modulation of heart rate, with other physiological influences on heart rate, as well. SDNN provides an estimate of the overall variability of HRV. The normal value for SDNN is 141 ± 39 ms (mean ± SD) and for SDANN 127 ± 35 ms (Task Force for the European Society of Cardiology and North American Society of Pacing and Electrophysiology 1996). Severely decreased SDNN, <50 ms, is associated with increased mortality in patients with myocardial infarction (MI), and in patients with chronic heart failure, when compared to SDNN >100 ms (Kleiger et al 1987, Nolan et al 1998).

4.7.6 Other cardiological measurements
Blood was sampled for cardiac enzymes creatine kinase (CK), creatine kinase MB-isoenzyme (CK-Mb), and troponin-T (TnT) at admission to ICU, and 6, 12, 18, 24, 36, 42, and 48 hours after the start of cooling or at respective time-points in the normothermia group and on the third, fourth, and seventh day after CA. Transthoracic ECHO (TTE) was performed to assess left ventricular systolic function at 24 to 30 hours after CA. The Simpson method was used to calculate ejection fraction (EF). The hypothermia-group patients were still hypothermic during the TTE. A second TTE was performed 14 days after CA. ECGs were recorded at
admission to ICU, 1, 2, 24, 30, 36, and 48 hours after the start of cooling and at 14 days after CA. Additionally, high-resolution ECG was recorded at admission to ICU, 1, 2, and 24 hours after the start of cooling and 14 days after CA. Data on cardiac enzymes are presented only in part in this thesis; no ECG and high-resolution ECG findings are presented.

A cardiologist, after reviewing all patient data, classified the cause of CA as acute MI, myocardial ischemia without infarction, primary arrhythmia, or unknown. Acute MI was defined according the guidelines of the Joint European Society of Cardiology and the American College of Cardiology Committee as a typical rise and gradual fall of serum TnT or CK-Mb with at least one of the following: ischemic symptoms, development of pathological Q-waves in ECG, ST-segment elevation or depression in ECG or coronary artery intervention; or as pathologic findings of an acute MI (The Joint European Society of Cardiology/American College of Cardiology Committee 2000). Acute ischemia without infarction was defined as ECG changes indicative of myocardial ischemia: ST-segment elevation or ST-segment depression or T-wave abnormalities only, without elevation of serum TnT or CK-Mb. The cause of CA, when it did not fulfill these criteria, was classified as primary arrhythmia.

4.7.7 Assessment of cognitive function

A comprehensive neuropsychological examination was performed 3 months after the CA. In statistical analyses a reduced number of test variables was used and grouped according to three functional domains. General cognitive capacity was estimated by the information subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler 1981). The learning and memory domain was evaluated by immediate and delayed retrieval on the logical memory test from the Wechsler Memory Scale-Revised (WMS-R) (Wechsler 1987), the fifth retrieval score and 20-minute delayed reproduction score of the Auditory Verbal Learning Test (AVLT), and by the picture recognition task of the Rivermead Behavioural Memory Test (Lezak et al 2004). Executive functioning was measured with the interference task of the modified Stroop test (50 items), the Trail-Making test (form B), the Verbal Fluency task (one minute generation of words beginning with the letter K), and with a timed calculation task (Lezak et al 2004). Speed of performance was estimated with the Digit symbol subtask of the WAIS-R, the Trail-Making test (form A), with the color naming of the modified Stroop test (50 items), and with the grooved pegboard task (dominant hand score) (Lezak et al, 2004). Depressive symptoms were evaluated by a short form of the Beck Depression Inventory (Beck and Beck, 1972). Neuropsychologist Erja Poutiainen, PhD, who examined the patients and analyzed the test results, was blinded to treatment group.

In addition to group analyses, cognitive deficit scores were calculated by means of age-corrected normative data derived from Finnish
population norms. Memory tests available for the deficit score analysis were the immediate and delayed retrieval of the WMS-R (Wechsler 1987, Ylikoski et al 1989). Deficit scores for executive function were derived from the Trail-Making-form B, the interference part of the modified Stroop test, and the verbal fluency task (Kontiola et al 1990, Poutiainen et al 2006, Rosti et al 2006), and for speed of performance from the Trail-making-Form A, the naming part of the modified Stroop task, and the Digit Symbol task of the WAIS-R (Poutiainen et al 2006, Rosti et al 2006, Wechsler 1981). The cut-point of 1.5 SD below the normative data served as a criterion for impaired cognitive performance on any particular test. A patient's performance was considered as intact or showing only subtle cognitive deficits if more than 70% (6 of the 8 tests) of the test scores were above the cut-point. Moderate impairment meant that 30 to 60% of the tests (3-4 tests) were below the cut-point, and severe impairment was meant more than 60% (5–8 tests) of the tests were below the cut-point. Cognitive functions were considered impaired if half the tests measuring a particular domain fell below the cut-point.

4.7.8 Quantitative EEG and auditory evoked P300 potential
The recording of Q-EEG was performed in a quiet and dim room. Each subject lay in a comfortable bed with eyes closed, but were urged to stay awake. EEG was recorded with 21 channels. For quantitative analysis, 24 epochs lasting 2.5 seconds each were gathered (1 minute). The chosen epochs had to be artifact-free, and without signs of any lowered level of vigilance in the EEG or electro-oculography channels during the recording. The analyzed frequency band was divided into a delta band (1.5–3.5 Hz), theta band (3.5–7.5 Hz), alpha band (7.5–12.5 Hz), and beta band (12.5–25.0 Hz). In monopolar montages (A1A2 as reference), absolute and relative power values were analyzed in these bands in all 21 channels. Mean frequencies within the whole 1.5 to 25 Hz frequency band was analyzed in all channels. The number of variables was reduced by calculation of 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). After these calculations there were 36 EEG variables (16 for absolute power, 16 for relative power and 4 for mean frequencies). This method has been described in detail previously (Riihimäki et al 2000).

Auditory evoked P300 potential was recorded while the subjects were awake, eyes closed and sitting back in a comfortable chair. The stimulation frequency was 0.50 to 0.58 Hz. Tones were presented binaurally. The standard tone frequency was 1000 Hz, and the target tone frequency was 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 targets. Activity was recorded at Cz and Pz electrode
sites of the 10–20 International System, referred to linked earlobes. The filter bandpass was 0.5 to 70 Hz. Analysis time was 650 ms, including a 50-ms pre-stimulus baseline. Latencies and amplitudes were measured afterwards. At first, mean responses were formed from the two original responses in the Pz channel. These mean responses were then filtered digitally (6 Hz low-pass filter). The latencies and amplitudes were measured from the filtered mean responses. In the amplitude measurements, the pre-stimulus baseline served as the reference level. The Q-EEGs and P300 potentials were analyzed by neurophysiologist Tero Kovala, MD, PhD, who was blinded to the patient’s treatment assignment.

Table 2 presents the timetable of measurements performed.
Table 2. Timeline and summary of measurements performed on HACA patients in Helsinki

**Admission to emergency room:**
- Screening for the trial

**Admission to ICU:**
- Randomization (Study I)
- Start of medication: midazolam, fentanyl, pancuronium
- Start of cooling in patients assigned to hypothermia
- ECG, high-resolution ECG, Lab I: CK, CK-Mb, TnT
- Start of 0- to 24-h ambulatory ECG recording (Study IV)

1 h after admission to ICU: ECG, high-resolution ECG
2 h after admission to ICU: ECG, high-resolution ECG
6 h after admission to ICU: Lab I
12 h after admission to ICU: Lab I
18 h after admission to ICU: Lab I
24 h after ROSC: Lab II: NSE, S-100B (Study II)

**24 h after admission to ICU:**
- Start of rewarming in hypothermia-assigned patients
- ECG, high-resolution ECG, Lab I
- Start of 24- to 48-h ambulatory ECG recording (Study IV)

24-28 h after ROSC: SEP and BAEP recordings (Study III)
24-30 h after ROSC: Transthoracic ECHO
30 h after admission to ICU: ECG

**32 h after admission to ICU:**
- Pancuronium discontinued in normothermia-assigned patients; in hypothermia-assigned patients pancuronium discontinued at 35°C

**36 h after ROSC: Lab II (Study II)**
36 h after admission to ICU: ECG, Lab I
42 h after admission to ICU: Lab I
48 h after ROSC: Lab II (Study II)

**48 h after admission to ICU:**
- ECG, Lab I
- Clinical evaluation: GCS, brain stem reflexes, the best-achieved CPC and OPC
3 days after CA: Lab I
4 days after CA: Lab I
7 days after CA:
- Lab I
- Clinical evaluation: GCS, brain stem reflexes, the best-achieved CPC and OPC
14 days after CA:
- 24-h ambulatory ECG recording (Study IV)
- ECG, high-resolution ECG
- Transthoracic ECHO

**Discharge from hospital:**
- Clinical evaluation: GCS, brain stem reflexes, the best-achieved CPC and OPC
3 months after CA:
- Evaluation of outcome
- Neuropsychological testing (Study V)
- Q-EEG and P300 recordings (Study V)
6 months after CA:
- Evaluation of outcome (Study I)

Mean delay from CA to ROSC was 18 min. Mean delay from CA to admission to ICU and start of cooling or maintaining normothermia was 3 h and 27 min. Lab I = serum CK, CK-Mb and TnT; Lab II = serum NSE and S-100B. ICU = Intensive care unit, ECG = electrocardiography, ROSC = restoration of spontaneous circulation, NSE = neuron-specific enolase, SEP = sensory evoked potentials, BAEP = brain stem auditory evoked potentials, GCS = Glasgow Coma Scale, CPC = Cerebral Performance Category, OPC = Overall Performance Category, CA = cardiac arrest, Q-EEG = quantitative electroencephalography
4.8 Statistical analyses

Categorical variables are given as counts and percentages. Data are given as median and range for non-normally distributed variables and as mean and SD for variables with a normal distribution.

Continuous data were compared with the Mann-Whitney U-test or t-test. Outcome data are binary, and the chi-square test or Fisher’s exact test was used to compare proportions between hypothermia and normothermia groups.

NSE- and S-100B levels and the time-course of cardiac enzymes in the hypothermia and normothermia groups were compared with repeated measures analysis of variance (ANOVA) after logarithmic transformation. The discriminative power of serum NSE and S-100B in predicting poor outcome was evaluated by receiver-operating characteristics (ROC) analysis. Cognitive functions were analyzed with MANOVAs and subsequent ANOVAs. Correlations were analyzed by Spearman’s rho-test. Multivariate analysis was performed with a logistic regression model (backward stepwise) with good outcome, and mortality at 6 months as the dependent variable. P values < 0.05 were considered statistically significant.

We used the Statistica data analysis software system* (StatSoft, Tulsa, OK, USA) to analyze the demographical, evoked potential, and cardiological data. Statistical software StatsDirect® (StatsDirect Ltd, Altrincham, Cheshire, UK) was used to analyze the data in the serum marker study, and the SPSS 13.0 data analysis software system (SPSS Inc. Chicago, IL, USA) to analyze the cognitive data and for multivariate analysis.
5 RESULTS

5.1 Results of the HACA trial (Study I)

Altogether 275 comatose CA survivors were randomized to the HACA study, 137 assigned to hypothermia treatment and 138 to normothermia. The enrollment rate was lower than expected in all centers participating in the HACA trial. Baseline characteristics for the two treatment groups were comparable, although the patients assigned to normothermia were more likely to have had a history of diabetes mellitus or coronary heart disease. They had also received bystander-initiated CPR slightly more often. The median interval between ROSC and initiation of cooling was 105 minutes, and the median interval between ROSC and achievement of the target core temperature (32–34ºC) was 8 hours. The majority of hypothermia-group patients also received ice-packs to speed cooling. Hypothermia was discontinued early in 14 patients. In the majority of these cases, the reason was patient death.

One patient in each group was lost to neurological follow-up. At 6 months after CA, of 136, 75 (55%) in the hypothermia group had achieved a good neurological outcome, defined as CPC 1 or 2. In the 137 normothermia group, 54 (39%) had a favorable neurological outcome (p=0.009; risk ratio 1.40, 95% CI 1.08–1.81). At 6 months after CA, of the 137 patients in the hypothermia group 56 (41%), and 76 (55%) of the 138 patients in the normothermia group had died (p=0.020; risk ratio 0.74, 95% CI 0.58–0.95). Based on these results, six patients (95% CI 4–25) would need to be treated with hypothermia to prevent one unfavorable outcome, and to prevent one death, seven patients (95% CI 4–33).

Bleeding of any severity, pneumonia, sepsis, pancreatitis, renal failure, pulmonary edema, seizures, arrhythmias, and pressure sores within the first 7 days were recorded. In the hypothermia group of 135, 98 (73%) patients had at least one complication, and in the normothermia group of 132, the respective figure was 93 (70%) (p=0.70). The rate of pneumonia and sepsis was higher in the hypothermia-treated group, but these differences were not significant.
5.2 Results of Helsinki HACA patients (Studies II–V)

5.2.1 Demographic and clinical characteristics of enrolled patients

Characteristics of the 36 hypothermia-treated and 34 normothermia-treated patients are presented in Table 3, and their medical history in Table 4. Median age was 59 years (range 18–75), and 80% of were men. All patients were independent prior to their arrest; 31% of all patients were employed at the time of the arrest, and one patient was still a student. Cardiac disorders were common, having occurred in half of the patients (coronary heart disease, cardiomyopathy, valvular heart disease or chronic atrial fibrillation). One of the study patients had been previously resuscitated from CA.

All patients were intubated and ventilated on arrival at the emergency room. Their blood chemistry on admission is presented in Table 5. No significant differences appeared in any of the baseline characteristics or in any treatment options prior to admission to the emergency department between the two treatment arms. The two treatment groups were comparable also in regard to laboratory data on admission, although pCO2 levels at admission were lower in the normothermia-treated group. Severe hypocapnia (pCO2 below 4.0 kPa) was detected in two subjects later randomized to hypothermia and in six subjects later randomized to normothermia treatment (p=0.080).

Table 3. Demographic and clinical characteristics of enrolled patients with cardiac arrest

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>36</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Male/female , N (%)</td>
<td>32/4 (89/11)</td>
<td>24/10 (71/29)</td>
<td>0.075</td>
</tr>
<tr>
<td>Age, years</td>
<td>60 (23–75)</td>
<td>59 (18–75)</td>
<td>0.400</td>
</tr>
<tr>
<td>Bystander-initiated CPR, N (%)</td>
<td>18 (50)</td>
<td>19 (56)</td>
<td>0.641</td>
</tr>
<tr>
<td>BLS, minutes</td>
<td>7.0 (5–14)</td>
<td>7.0 (5–11)</td>
<td>0.766</td>
</tr>
<tr>
<td>ACLS, minutes</td>
<td>14.0 (5–59)</td>
<td>13.0 (5–39)</td>
<td>0.316</td>
</tr>
<tr>
<td>ROSC, minutes</td>
<td>18.0 (9–39)</td>
<td>18.5 (8–45)</td>
<td>0.791</td>
</tr>
<tr>
<td>Number of defibrillations before ROSC</td>
<td>3 (1–12)</td>
<td>2 (1–30)</td>
<td>0.285</td>
</tr>
<tr>
<td>Total dose of epinephrine before ROSC, mg</td>
<td>2.0 (0–9.0)</td>
<td>2.0 (0–6.5)</td>
<td>0.328</td>
</tr>
<tr>
<td>Thrombolysis, N (%)</td>
<td>13 (36)</td>
<td>9 (26)</td>
<td>0.446</td>
</tr>
<tr>
<td>Tympanic temperature at admission, °C</td>
<td>35.2 (33.4–36.9)</td>
<td>35.5 (33.6–36.9)</td>
<td>0.797</td>
</tr>
<tr>
<td>Glasgow Coma Scale at admission</td>
<td>5 (3–7)</td>
<td>5 (3–8)</td>
<td>0.416</td>
</tr>
</tbody>
</table>

Data given as absolute numbers and percentages or as median and range. CPR = cardiopulmonary resuscitation, BLS = basic life support, ACLS = advanced cardiac life support, ROSC = restoration of spontaneous circulation
### Table 4. Medical history of cardiac arrest patients (previous diagnoses)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>N=36</td>
<td>N=34</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>8 (22%)</td>
<td>8 (23%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>13 (36%)</td>
<td>15 (44%)</td>
<td>0.626</td>
</tr>
<tr>
<td>Previous acute MI</td>
<td>7 (19%)</td>
<td>10 (29%)</td>
<td>0.408</td>
</tr>
<tr>
<td>Previous CAGB</td>
<td>5 (14%)</td>
<td>5 (15%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>7 (19%)</td>
<td>5 (15%)</td>
<td>0.754</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>3 (8%)</td>
<td>2 (6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Chronic atrial fibrillation</td>
<td>2 (6%)</td>
<td>7 (21%)</td>
<td>0.080</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (3%)</td>
<td>6 (18%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>0</td>
<td>2 (6%)</td>
<td>0.232</td>
</tr>
<tr>
<td>Smoker</td>
<td>16 (44%)</td>
<td>11 (32%)</td>
<td>0.335</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>3 (8%)</td>
<td>4 (12%)</td>
<td>0.706</td>
</tr>
</tbody>
</table>

Data given as absolute numbers and percentages. Fisher's two-tailed exact test served for comparisons between groups. MI = myocardial infarction, CAGB = coronary artery bypass grafting.

### Table 5. Blood chemistry of cardiac arrest patients on admission to emergency room

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>N=36</td>
<td>N=34</td>
<td></td>
</tr>
<tr>
<td>pO2, kPa</td>
<td>16.3 (7.6–59.5)</td>
<td>21.0 (7.2–56.8)</td>
<td>0.301</td>
</tr>
<tr>
<td>pCO2, kPa</td>
<td>5.4 (3.0–9.1)</td>
<td>5.1 (1.9–7.2)</td>
<td>0.025</td>
</tr>
<tr>
<td>pH</td>
<td>7.32 (7.12–7.49)</td>
<td>7.33 (6.9–7.53)</td>
<td>0.160</td>
</tr>
<tr>
<td>Base excess, mmol/L</td>
<td>-5.6 (-16.8–1.2)</td>
<td>-5.1 (-28.8–1.8)</td>
<td>0.749</td>
</tr>
<tr>
<td>HCO3, mmol/L</td>
<td>20 (12–26)</td>
<td>20 (5–26)</td>
<td>0.755</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>142 (104–171)</td>
<td>143 (114–168)</td>
<td>0.694</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>41 (31–50)</td>
<td>41 (34–47)</td>
<td>0.862</td>
</tr>
<tr>
<td>Thrombocytes, E9/L</td>
<td>199 (129–461)</td>
<td>239 (48–326)</td>
<td>0.206</td>
</tr>
<tr>
<td>Leukocytes, E9/L</td>
<td>11.2 (5.9–23.3)</td>
<td>10.3 (4.9–21.9)</td>
<td>0.747</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>10.3 (6.1–18.7)</td>
<td>9.7 (1.9–25.9)</td>
<td>0.378</td>
</tr>
<tr>
<td>Sodium, mmol/L</td>
<td>139 (134–144)</td>
<td>140 (118–147)</td>
<td>0.723</td>
</tr>
<tr>
<td>Potassium, mmol/l</td>
<td>4.2 (3.0–6.1)</td>
<td>3.9 (3.1–5.3)</td>
<td>0.079</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>102 (69–158)</td>
<td>99 (70–163)</td>
<td>0.425</td>
</tr>
<tr>
<td>CK, u/L</td>
<td>275 (66–6059)</td>
<td>179 (49–1170)</td>
<td>0.054</td>
</tr>
<tr>
<td>CK-MB, μg/L</td>
<td>10 (2–370)</td>
<td>6 (1–121)</td>
<td>0.208</td>
</tr>
</tbody>
</table>

Data given as median and range.
5.2.2 ICU treatment

Cooling was started in the ICU, but in two cases in the emergency department, due to a delay in transferral to the ICU. The mean time from CA to admission to ICU and start of cooling or maintenance of normothermia was 3 hours and 27 minutes (SD 49 minutes). The temperature curves for both groups are presented in Figure 4. In the hypothermia group, mean time from CA to achievement of the target temperature (core temperature below 34ºC) was 7 hours and 40 minutes (SD 2 hours and 40 minutes). Passive rewarming was ineffective in most hypothermia-assigned patients, and mild external warming was usually needed in the early rewarming phase.

Figure 4. Core temperatures of patient groups during the first 48 hours after cardiac arrest. First temperature recorded on admission (adm) to emergency room. X-axis: time in hours, Y-axis: core temperature, ºC.

Treatment groups were comparable concerning treatment in the ICU. Protocol-related medications, inotropic agents, fluids, and urine values are presented in Table 6, and other medications in Table 7. Table 8 presents electrolyte levels for 48 hours.
Table 6. Total doses of protocol-related medications, inotropic agents, iv-fluids, and urine output during the first 48 hours after cardiac arrest

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=36</td>
<td>N=34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine, mg</td>
<td>608 (647)</td>
<td>557 (578)</td>
<td>0.933</td>
</tr>
<tr>
<td>Dobutamine, mg</td>
<td>191 (412)</td>
<td>78 (184)</td>
<td>0.100</td>
</tr>
<tr>
<td>Norepinephrine, mg</td>
<td>1.0 (3.2)</td>
<td>0.7 (2.4)</td>
<td>0.586</td>
</tr>
<tr>
<td>Epinephrine, mg</td>
<td>0.9 (3.0)</td>
<td>0.3 (1.7)</td>
<td>0.196</td>
</tr>
<tr>
<td>Midazolam, mg</td>
<td>322 (63)</td>
<td>307 (163)</td>
<td>0.030</td>
</tr>
<tr>
<td>Fentanyl, mg</td>
<td>6.09 (1.2)</td>
<td>6.15 (2.1)</td>
<td>0.549</td>
</tr>
<tr>
<td>Pancuronium, mg</td>
<td>63.1 (24.6)</td>
<td>50.2 (31.3)</td>
<td>0.139</td>
</tr>
<tr>
<td>Insulin, IU</td>
<td>19 (88)</td>
<td>22 (47)</td>
<td>0.319</td>
</tr>
<tr>
<td>Fluids iv, mL</td>
<td>12630 (2770)</td>
<td>10480 (1910)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine output, mL</td>
<td>6610 (2290)</td>
<td>5450 (1820)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Data given as mean and SD.

Table 7. Additional medications administered during the first 48 hours after cardiac arrest

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=36</td>
<td>N=34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetosalisylic acid</td>
<td>21 (58%)</td>
<td>21 (62%)</td>
<td>0.811</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>23 (64%)</td>
<td>25 (74%)</td>
<td>0.803</td>
</tr>
<tr>
<td>Unfractioned heparin</td>
<td>9 (25%)</td>
<td>5 (15%)</td>
<td>0.374</td>
</tr>
<tr>
<td>Betablocking agent</td>
<td>34 (94%)</td>
<td>30 (88%)</td>
<td>0.422</td>
</tr>
<tr>
<td>Antiarrhythmic medication</td>
<td>18 (50%)</td>
<td>13 (38%)</td>
<td>0.347</td>
</tr>
<tr>
<td>Anticonvulsive medication</td>
<td>2 (6%)</td>
<td>5 (15%)</td>
<td>0.253</td>
</tr>
<tr>
<td>Diuretics</td>
<td>33 (92%)</td>
<td>31 (91%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>2 (6%)</td>
<td>6 (18%)</td>
<td>0.146</td>
</tr>
<tr>
<td>Steroids</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
<td>0.609</td>
</tr>
</tbody>
</table>

Data given as absolute numbers and percentages. Fisher's two-tailed exact test was used for comparisons between the groups.
Table 8. Electrolyte levels during the first 48 hours after cardiac arrest

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia N=36</th>
<th>Normothermia N=34</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma potassium, mmol/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 12 h</td>
<td>3.9 (0.3)</td>
<td>4.0 (0.5)</td>
<td>0.596</td>
</tr>
<tr>
<td>24 h</td>
<td>4.2 (0.5)</td>
<td>4.1 (0.3)</td>
<td>0.129</td>
</tr>
<tr>
<td>36 h</td>
<td>4.6 (0.6)</td>
<td>4.1 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>48 h</td>
<td>4.2 (0.4)</td>
<td>4.0 (0.3)</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Plasma sodium, mmol/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 12 h</td>
<td>138 (2.6)</td>
<td>139 (3.9)</td>
<td>0.117</td>
</tr>
<tr>
<td>24 h</td>
<td>139 (2.6)</td>
<td>139 (3.8)</td>
<td>0.985</td>
</tr>
<tr>
<td>36 h</td>
<td>140 (3.2)</td>
<td>138 (3.4)</td>
<td>0.171</td>
</tr>
<tr>
<td>48 h</td>
<td>138 (3.6)</td>
<td>138 (3.7)</td>
<td>0.101</td>
</tr>
</tbody>
</table>

Data given as mean and SD.

The median duration of ICU treatment was 4.5 days (range 1–15 days) in the hypothermia group and 3 days (range 1–32) in the normothermia group (p=0.04). From the ICU the majority of patients were transferred to a step-down ICU. The Meilahti step-down ICU (ward 22) has facilities for standard intensive care and monitoring including mechanical ventilation, arterial catheters, and central venous catheters. When the duration of treatment in the ICU and step-down ICU were totalled, no significant difference emerged as to duration of treatment (median 5.5 days in hypothermia and 6 days in normothermia group, p=0.57).

5.2.3 Complications of treatment

Adverse events occurring during the first 7 days after CA were recorded. In the hypothermia group, 27 (75%) patients had pneumonia, defined by typical changes in chest X-ray, elevation of C-reactive protein, and i.v. antibiotics prescribed. In the normothermia group, the respective number was 22 (65%). Sepsis was diagnosed in two (6%) hypothermia-treated and five (15%) normothermia-treated patients.

Minor bleeding (defined as bleeding from mucous membranes, nose, urinary tract, or root of catheter, not requiring treatment) was observed in 13 (36%) hypothermia-treated patients; 8 of these had received thrombolysis for acute MI, and the rest, low-molecular-weight heparin (LMWH) and asetylsalicylic acid. One (3%) hypothermia-treated patient had clinically significant bleeding from a nasogastric tube and received 6 units of packed red cells and 500 ml of fresh frozen plasma to control the bleeding. This patient had not received thrombolysis, but had been on warfarin before
the incident. In the normothermia group, minor bleeding occurred in nine (26%) patients: Three of them had received thrombolysis, four were on warfarin, and two had received LMWH. No clinically significant bleeding was observed in normothermia-treated patients.

Metabolic acidosis occurred in one (3%) patient in each group. Renal failure was observed in two (6%) normothermia-group patients. None of these differences were significant. The arrhythmic adverse effects are described in section 5.2.7.

5.2.4 Outcome

Of all 70 patients, 50 regained consciousness (29 hypothermia, 21 normothermia, p=0.082). Only seven patients recovered consciousness during the first 48 hours (4 hypothermia, 3 normothermia), and at 48 hours, most patients (90%) were still anesthetized or sedated and mechanically ventilated. Some of our patients did not recover consciousness until day 5 after CA, but made a good recovery thereafter. Only one of the patients (hypothermia group) experienced a major neurological complication after recovery of consciousness. This patient had a secondarily generalized status epilepticus and later severe cognitive deficits in the neuropsychological examination.

At 6 months after CA, outcome was favorable (CPC 1 or 2) in 69% (N=25) of hypothermia-treated patients and in 47% (N=16) of those normothermia-treated (p=0.057). In the hypothermia group, nine patients (25%) died after a median of 13 days (range, 1–116 days). In the normothermia group, 13 patients (38%) died after a median of 9 days (range, 1–147 days) (p=0.233). Only one patient in the hypothermia group died within 6 months after primarily achieving a good CPC (Table 9).

The reason for death in the hypothermia-treated group was neurologic in five (56%) subjects, cardiovascular in three (33%), and from multiple organ failure in one (11%). In the normothermia-treated group, death was neurologic in nine subjects (69%), cardiovascular in two (15%) and from multiple organ failure in two (15%).

At 3 months after CA, 25 patients in the hypothermia-treated group and 17 patients in the normothermia-treated group lived at home. One of the former and two of the latter lived alone; all others lived with a spouse or other close relative. In the hypothermia group, two patients attended daytime care for rehabilitation twice a week, and one patient who took care of her disabled husband received some domestic help twice a week. One normothermia-group patient had a personal assistant at home. At 6 months after CA, none of the 42 home-living patients (25 hypothermia, 17 normothermia) received any domestic help from the social home-care system or attended daytime care. Four patients (two in each groups) then lived alone.

Eight patients (three hypothermia, five normothermia) were in institutional care at 3 months after CA; at 6 months, only five patients
needed long-term institutional care (one and four patients, respectively), and one hypothermia-group patient was in a rehabilitation facility, but was a little later discharged home.

At the time of CA, 23 patients were employed. At 6 months after CA, seven hypothermia patients had returned to their previous employment, one was still on sick-leave, and three had retired from their previous work due to the event. In the normothermia group, six patients had returned to their previous work, and six patients were retired.

<table>
<thead>
<tr>
<th>Table 9. Outcome of study patients 6 months after cardiac arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia N=36</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td><strong>Cerebral Performance Category (CPC)</strong></td>
</tr>
<tr>
<td>CPC 1</td>
</tr>
<tr>
<td>CPC 2</td>
</tr>
<tr>
<td>CPC 3</td>
</tr>
<tr>
<td>CPC 4</td>
</tr>
<tr>
<td>CPC 5</td>
</tr>
<tr>
<td><strong>Good outcome (CPC 1 or 2)</strong></td>
</tr>
<tr>
<td><strong>Poor outcome (CPC 3, 4, or 5)</strong></td>
</tr>
<tr>
<td><strong>Death (CPC 5)</strong></td>
</tr>
<tr>
<td><strong>No change in pre-arrest CPC</strong></td>
</tr>
<tr>
<td><strong>Living at home</strong></td>
</tr>
<tr>
<td><strong>Rehabilitation facility</strong></td>
</tr>
<tr>
<td><strong>Institutionalized</strong></td>
</tr>
</tbody>
</table>

Data given as absolute numbers and percentages.

Those with good recovery potential had cardiological diagnostic examinations and therapeutic interventions generally performed during their initial hospital stay. Coronary angiography was performed on 23 (64%) patients in the hypothermia group and 12 (35%) patients in the normothermia group. In only one subject was the angiography performed before the ICU treatment. Coronary artery bypass grafting (CABG) was performed on 11 (31%) and 4 (12%) patients, and percutaneous coronary intervention (PCI) on 6 (17%) and 5 (15%). Electrophysiological testing was performed on 10 (28%) hypothermia-treated and 7 (21%) normothermia-treated patients and an implantable cardioverter defibrillator (ICD) was implanted in 3 (8%) and 5 (15%).
The etiology of CA in the hypothermia and normothermia groups was acute MI in 24 patients (67%) and 21 patients (62%), ischemia in 5 (14%) and 3 (9%), and primary arrhythmia in 7 (19%) and 10 patients (29%), respectively.

### 5.2.5 Serum NSE- and S-100B findings (Study II)

Since two patients died before 24 hours, serum NSE and S-100B could be measured in 35 hypothermic patients and 33 normothermic patients. From some patients, blood samples were not available at every time-point. The difference in NSE values between 24 and 48 hours could be analyzed in 34 hypothermic and in 32 normothermic patients, and the difference in serum S-100B values in 34 and in 32 patients, respectively.

Levels of NSE were lower in the hypothermia group than in the normothermia group (P=0.007, by ANOVA for repeated measurements). A decrease in NSE values between 24 and 48 hours occurred in 30 of 34 patients (88%) in the hypothermia group and in 16 of 32 patients (50%) in the normothermia group (p<0.001). This decrease was associated with good outcome and an increase with poor outcome at 6 months after CA (p=0.005). The decrease in NSE values was also associated with regaining consciousness (p<0.001), with no change in pre-arrest CPC (p<0.001), and with survival for at least 6 months after ROSC (p=0.012). The hypothermia-treated patients with good outcome (CPC 1 or 2) had significantly higher NSE values at 24 hours after CA than did patients with good outcome in the normothermia group (median 10.0 vs 6.3 μg/L, p<0.001).

Levels of serum S-100B between the two treatment arms did not differ. Serum S-100B levels decreased between 24 and 48 hours in 17 (50%) of the 34 patients in the hypothermia group and in 15 (45%) of the 33 patients in the normothermia group. The decrease in levels of serum S-100B during this time-period was unrelated to outcome.

The ROC analysis of serum NSE and S-100B at different time-points revealed that cut-off values predicting unfavorable outcome with a specificity of at least 95% were higher in the hypothermia group; unfortunately, the sensitivity of these tests was remarkably poor in the hypothermia group.

### 5.2.6 Sensory and brain stem auditory evoked potential findings (Study III)

**SEP**

Nerve conduction velocity was significantly lower in the hypothermia group (median 46.2 vs 53.5 m/s, p<0.001). A cervical N13 peak was detected in all patients. The cervicocortical conduction time (time from cervicomedullary N13 to cortical N20) was significantly higher and latencies to cervicocortical N13 response and to early cortical N20 response were significantly longer in the hypothermia group (p<0.001). In hypothermic patients, the cortical N20 response appeared approximately 24 ms after
the stimulus. No clear effect of hypothermia of 33ºC on amplitudes of the cortical responses appeared: Amplitudes of N20 responses in the two treatment groups were comparable, and amplitudes of N20 response did not correlate with outcome.

Cortical N20 responses were bilaterally absent in 11 patients, 3 in the hypothermia group and 8 in the normothermia group. None of these 11 patients regained consciousness, and all died after a median of 10 days (range 2–354 days). Bilaterally absent cortical N20 responses predicted permanent coma with a specificity of 100% (95% CI 92–100%). Three patients had bilateral N20 responses but did not awaken (one hypothermia and two normothermia). Sensitivity was thus a respective 75% (95% CI 30–95%) and 80% (95% CI 49–94%). Figure 5 shows an example of normal cortical N20 responses and Figure 6 an example of bilaterally absent cortical N20 responses.

Figure 5. SEP recording with normal cortical N20 responses
BAEP
All the latencies of wave I, III, and V responses were significantly longer in those hypothermia-treated (p<0.02-0.001), as were also the interpeak interval latencies of I–III, III–V, and I–V waves (p<0.001). Within the treatment groups, latencies did not correlate with age, with awakening, or with achieving a favorable outcome. At least one of the waveforms: I, III, or V was consistently missing in two hypothermia-treated and four normothermia-treated patients. In two patients, these responses were missing only unilaterally; each patient was known to have a hearing loss and awakened later. In four patients, these responses were missing bilaterally, and three of them did not regain consciousness. The one patient who awakened despite bilaterally missing waveforms had a hearing deficit and used a hearing aid. In this study, the addition of BAEP recording to SEP did not result in improved sensitivity in identifying patients with a poor prognosis, as compared to SEP recording alone.

5.2.7 Ambulatory ECG findings (Study IV)
The results of the Holter analyses are presented in Table 10. The mean heart rate was significantly lower in the hypothermia group during the first two recordings. The number of isolated PVBs, of bigeminy, and of couplets was higher in the hypothermia group during the first and second recording; the number of ventricular runs was also higher in the hypothermia group in both the first and second recording. Ventricular runs lasting longer than 30...
seconds occurred in three hypothermia patients and in one normothermia patient. The majority of the ventricular runs were monomorphic; polymorphic runs occurred in at least one recording in four hypothermia and two normothermia patients. Number of VTs or VF s between the groups did not differ. No significant differences arose in the occurrence of SVPB during the first 2 days after CA, but the number of supraventricular runs was slightly higher in the normothermia group during the first recording. At 14 days after CA, no significant differences in these Holter parameters appeared between groups.

VT requiring direct current cardioversion occurred in three patients: in two hypothermia-group patients before the induction of hypothermia (T bladder over 37°C in both cases) and in one normothermia-group patient. Supraventricular tachycardia requiring pharmacological treatment or cardioversion occurred in two patients in each group, but in only one patient during actual hypothermia. VF occurred in three patients randomized to hypothermia and in one patient randomized to normothermia. In one hypothermia patient with a large anterior MI, VF occurred twice in the final phase of cardiogenic shock during actual hypothermia (T bladder 32.3°C); this patient could not be resuscitated from the second VF and died. In another patient randomized to hypothermia, VF occurred just after transfer to the ICU and prior to the induction of hypothermia (T bladder 36.0°C); this patient also had VF and several VTs on the third day after CA and needed emergency CABG, but made an excellent recovery thereafter. The third hypothermia-group patient had VF during the second recording, after the rewarming phase (T bladder 38.0°C). In this patient, etiology of CA was acute MI and subtotal occlusion of the left anterior descending coronary artery, which had been treated with PCI before induction of hypothermia. This patient made a good recovery and was discharged home with an ICD. In one normothermia-group patient, VF occurred once during the first 24-hour recording (T bladder 38.0°C) and was successfully treated. This patient’s etiology of CA was acute MI and severe three-vessel disease. After CABG, he made a good recovery.
<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0- to 24-h recording</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>minimum heart rate, BPM</td>
<td>50 (23–74)</td>
<td>59 (32–99)</td>
<td>0.002</td>
</tr>
<tr>
<td>mean heart rate, BPM</td>
<td>68 (37–97)</td>
<td>82 (58–119)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>maximum heart rate, BPM</td>
<td>105 (50–180)</td>
<td>132 (85–184)</td>
<td>0.036</td>
</tr>
<tr>
<td>maximum R-R, ms</td>
<td>1742 (1070–3625)</td>
<td>1367 (790–2280)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>maximum N-N, ms</td>
<td>1476 (882–2539)</td>
<td>1156 (617–1890)</td>
<td>0.015</td>
</tr>
<tr>
<td>PVB/hour</td>
<td>35.7 (0.6–1047.8)</td>
<td>7.6 (0.1–173.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of isolated PVBs</td>
<td>594 (14–23350)</td>
<td>123 (3–4070)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bigeminy</td>
<td>6 (0–4076)</td>
<td>0 (0–1302)</td>
<td>0.039</td>
</tr>
<tr>
<td>Number of couplets</td>
<td>13 (0–778)</td>
<td>5 (0–209)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of ventricular runs</td>
<td>10.5 (0–195)</td>
<td>2.5 (0–127)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of VTs</td>
<td>1 (0–146)</td>
<td>1(0–60)</td>
<td>0.685</td>
</tr>
<tr>
<td>Number of patients with at least one VT (%)</td>
<td>24 (67)</td>
<td>23 (74)</td>
<td>0.502</td>
</tr>
<tr>
<td>SVPB/hour</td>
<td>2.7 (0–125)</td>
<td>2.0 (0–397)</td>
<td>0.300</td>
</tr>
<tr>
<td>Number of SV runs</td>
<td>0 (0–53)</td>
<td>1 (0–231)</td>
<td>0.046</td>
</tr>
<tr>
<td>Number of patients with at least one SV run (%)</td>
<td>15 (41)</td>
<td>19 (55)</td>
<td>0.234</td>
</tr>
<tr>
<td><strong>24- to 48-h recording</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>minimum heart rate, BPM</td>
<td>54 (28–89)</td>
<td>66 (34–98)</td>
<td>0.004</td>
</tr>
<tr>
<td>mean heart rate, BPM</td>
<td>85 (57–130)</td>
<td>91 (65–121)</td>
<td>0.160</td>
</tr>
<tr>
<td>maximum heart rate, BPM</td>
<td>123 (91–211)</td>
<td>125 (94–187)</td>
<td>0.587</td>
</tr>
<tr>
<td>maximum R-R, ms</td>
<td>1450 (900–3085)</td>
<td>1253 (780–2400)</td>
<td>0.014</td>
</tr>
<tr>
<td>maximum N-N, ms</td>
<td>1243 (859–3085)</td>
<td>1020 (648–1828)</td>
<td>0.010</td>
</tr>
<tr>
<td>PVB/hour</td>
<td>19.5 (0.1–797.5)</td>
<td>3.7 (0–146.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of isolated PVBs</td>
<td>301 (2–18732)</td>
<td>87 (1–2580)</td>
<td>0.010</td>
</tr>
<tr>
<td>Bigeminy</td>
<td>0 (0–8299)</td>
<td>0 (0–218)</td>
<td>0.189</td>
</tr>
<tr>
<td>Number of couplets</td>
<td>0 (0–492)</td>
<td>1 (0–134)</td>
<td>0.021</td>
</tr>
<tr>
<td>Number of ventricular runs</td>
<td>2 (0–111)</td>
<td>0 (0–27)</td>
<td>0.026</td>
</tr>
<tr>
<td>Number of VTs</td>
<td>0.5 (0–104)</td>
<td>0 (0–27)</td>
<td>0.126</td>
</tr>
<tr>
<td>Number of patients with at least one VT (%)</td>
<td>17 (50)</td>
<td>10 (32)</td>
<td>0.147</td>
</tr>
<tr>
<td>SVPB/hour</td>
<td>2.2 (0–206)</td>
<td>1.4 (0–260)</td>
<td>0.545</td>
</tr>
<tr>
<td>Number of SV runs</td>
<td>0 (0–740)</td>
<td>1 (0–44)</td>
<td>0.374</td>
</tr>
</tbody>
</table>
### 5.2.8 Heart rate variability findings (Study IV)

HRV results for both treatment groups in Table 11 show that all the time-domain variables were significantly higher in the hypothermia group during the first 24 hours. On the first recording, SDNN was below 50 ms in none of the hypothermia patients and in five of the normothermia patients (p=0.019), indicating severely attenuated HRV. On the second recording, the respective numbers were one and seven (p=0.018). SDNN and SDANN were very significantly higher in the hypothermia group also on the second recording (24–48 hour), but rMSSD and pNN50 between the groups did not differ at this time-point. At 14 days after CA, none of these variables differed between groups. The frequency-domain variables showed a similar pattern. The total, low-frequency, and high-frequency power spectral bands were all significantly higher in the hypothermia group during the first recording. These values remained higher on the second recording, but without significant differences.
Table 11. Heart rate variability at 0 to 24 hours, 24 to 48 hours, and 14 days after cardiac arrest

<table>
<thead>
<tr>
<th></th>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>120 (50–332)</td>
<td>66 (27–181)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24–48 h</td>
<td>123 (38–362)</td>
<td>71 (33–150)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>14 days</td>
<td>75 (34–142)</td>
<td>69 (20–226)</td>
<td>0.358</td>
</tr>
<tr>
<td>SDANN, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>114 (49–293)</td>
<td>62 (26–211)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24–48 h</td>
<td>129 (38–368)</td>
<td>64 (32–140)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>14 days</td>
<td>64 (7–121)</td>
<td>65 (16–141)</td>
<td>0.766</td>
</tr>
<tr>
<td>rMSSD, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>20 (8–100)</td>
<td>11 (7–43)</td>
<td>0.010</td>
</tr>
<tr>
<td>24–48 h</td>
<td>15 (7–47)</td>
<td>11 (7–33)</td>
<td>0.334</td>
</tr>
<tr>
<td>14 days</td>
<td>18 (10–86)</td>
<td>14 (9–98)</td>
<td>0.318</td>
</tr>
<tr>
<td>pNN50, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>2.1 (0.0–30.3)</td>
<td>0.7 (0.0–22.5)</td>
<td>0.030</td>
</tr>
<tr>
<td>24–48 h</td>
<td>1.3 (0.0–13.1)</td>
<td>0.3 (0.0–12.0)</td>
<td>0.313</td>
</tr>
<tr>
<td>14 days</td>
<td>1.8 (0.1–34.2)</td>
<td>0.7 (0.0–54.5)</td>
<td>0.293</td>
</tr>
<tr>
<td>Total power, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>12.5 (4.0–28.0)</td>
<td>7.0 (4.0–28.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>24–48 h</td>
<td>12.0 (4.0–12.0)</td>
<td>9.0 (4.0–38.0)</td>
<td>0.630</td>
</tr>
<tr>
<td>14 days</td>
<td>21.0 (4.1–73.0)</td>
<td>15.5 (7.0–98.0)</td>
<td>0.402</td>
</tr>
<tr>
<td>LF, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>9.0 (3.0–34.0)</td>
<td>4.0 (2.0–22.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>24–48 h</td>
<td>6.5 (2.0–23.2)</td>
<td>5.0 (2.0–23.0)</td>
<td>0.653</td>
</tr>
<tr>
<td>14 days</td>
<td>12.5 (4.0–51.0)</td>
<td>9.0 (1.3–60.0)</td>
<td>0.083</td>
</tr>
<tr>
<td>HF, ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>6.0 (2.0–28.1)</td>
<td>3.0 (2.0–13.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>24–48 h</td>
<td>5.0 (2.0–16.0)</td>
<td>4.0 (2.0–14.1)</td>
<td>0.639</td>
</tr>
<tr>
<td>14 days</td>
<td>6.0 (3.0–33.0)</td>
<td>5.0 (3.0–39.0)</td>
<td>0.438</td>
</tr>
</tbody>
</table>

Data given as median and range. In the hypothermia group data are from 30 subjects (0–24-h and 24–48-h recordings) or from 26 subjects (14-day recordings). In the normothermia group data are from 27 subjects (0–24-h recordings), from 25 subjects (24–48-h recordings), or from 16 subjects (14-day) recordings.
In univariate analysis, the following HRV parameters were associated with outcome in the hypothermia group: SDNN (p=0.013), SDANN (p=0.018), and LF (p=0.029) of the 24- to 48-hour recording. In the normothermia group, none of the HRV parameters was associated with outcome.

5.2.9 Neuropsychological performance (Study V)
At 3 months after CA, 50 patients were alive (28 hypothermia, 22 normothermia, p=0.226) and a total of 20 patients had died. Three of these 50 (one hypothermia, two normothermia) were unconscious at 3 months after CA. Two normothermia patients (CPC 1 and CPC 2) were unable to attend the neurological studies due to long distances. Both of them lived alone and were independent in all activities of daily living functions, according to their report and reports of their closest relatives. Neuropsychological testing could thus be performed on 45 of the 47 conscious survivors of CA (27 hypothermia, 18 normothermia).

No significant differences emerged in any of the cognitive functions between the two groups. Analyses of cognitive deficit scores revealed that 18 (67%) of hypothermia-treated and 8 (44%) of normothermia-treated patients were cognitively intact or had only subtle deficits. Moderate cognitive deficits were found in five (19%) and five (28%) patients, respectively. Severe cognitive deficits were found in four (15%) of the hypothermia-treated and in five (28%) of the normothermia-treated group. Severe cognitive deficits indicating dementia and permanently affecting activities of daily living were found in four patients (two in each group). Although a trend appeared toward better cognitive outcome in the hypothermia group, the differences were not significant. In total, 33% of patients had deficits in executive functioning, 24% in learning and memory, and 19% in speed of performance. Poor performance in all the cognitive functions measured correlated significantly with high CPC values at 3 and 6 months after CA (p< 0.01). No correlation appeared between cognition and resuscitation delays.

5.2.10 Quantitative EEG and P-300 (Study V)
Of the 45 patients tested neuropsychologically, three (all in institutional care) refused it or were not eligible for the recording of Q-EEG and P300 potential. Thus, Q-EEG and P300 could be performed for only 42 patients (26 hypothermia, 16 normothermia). One Q-EEG recording failed due to a technical artefact, and two P300 recordings failed due to patient-related difficulties. The Q-EEGs of hypothermia patients included consistently more fast- and less slow-frequency activity in all brain regions and had a higher mean frequency in all regions, but these differences were not significant. The amplitude of the P-300 response was significantly higher in the hypothermia group (p=0.028) (Table 12).
<table>
<thead>
<tr>
<th>Hypothermia</th>
<th>Normothermia</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=25)</td>
<td>(N=16)</td>
<td></td>
</tr>
<tr>
<td>Absolute power of band</td>
<td></td>
<td></td>
</tr>
<tr>
<td>frontal delta</td>
<td>3.183 (1.325)</td>
<td>3.635 (2.008)</td>
</tr>
<tr>
<td>temporal delta</td>
<td>2.224 (1.467)</td>
<td>2.695 (2.000)</td>
</tr>
<tr>
<td>centroparietal delta</td>
<td>3.752 (2.546)</td>
<td>4.550 (3.282)</td>
</tr>
<tr>
<td>occipital delta</td>
<td>3.842 (3.481)</td>
<td>4.756 (3.375)</td>
</tr>
<tr>
<td>frontal theta</td>
<td>6.256 (4.812)</td>
<td>6.732 (4.251)</td>
</tr>
<tr>
<td>temporal theta</td>
<td>4.129 (4.137)</td>
<td>4.935 (3.911)</td>
</tr>
<tr>
<td>centroparietal theta</td>
<td>7.677 (8.386)</td>
<td>9.490 (7.150)</td>
</tr>
<tr>
<td>occipital theta</td>
<td>7.036 (9.986)</td>
<td>8.638 (7.431)</td>
</tr>
<tr>
<td>frontal alpha</td>
<td>14.450 (12.199)</td>
<td>11.839 (10.653)</td>
</tr>
<tr>
<td>temporal alpha</td>
<td>11.986 (10.218)</td>
<td>10.834 (7.845)</td>
</tr>
<tr>
<td>centroparietal alpha</td>
<td>21.481 (17.728)</td>
<td>18.632 (14.360)</td>
</tr>
<tr>
<td>occipital alpha</td>
<td>31.140 (26.582)</td>
<td>28.110 (17.876)</td>
</tr>
<tr>
<td>frontal beta</td>
<td>6.613 (3.425)</td>
<td>8.713 (11.248)</td>
</tr>
<tr>
<td>temporal beta</td>
<td>5.625 (3.221)</td>
<td>5.177 (2.386)</td>
</tr>
<tr>
<td>centroparietal beta</td>
<td>9.534 (5.998)</td>
<td>8.053 (4.079)</td>
</tr>
<tr>
<td>occipital beta</td>
<td>8.059 (5.527)</td>
<td>6.906 (2.673)</td>
</tr>
<tr>
<td>Relative power of band</td>
<td></td>
<td></td>
</tr>
<tr>
<td>frontal delta</td>
<td>12% (0.042)</td>
<td>13% (0.037)</td>
</tr>
<tr>
<td>temporal delta</td>
<td>11% (0.042)</td>
<td>12% (0.034)</td>
</tr>
<tr>
<td>centroparietal delta</td>
<td>10% (0.043)</td>
<td>11% (0.034)</td>
</tr>
<tr>
<td>occipital delta</td>
<td>9% (0.045)</td>
<td>10% (0.034)</td>
</tr>
<tr>
<td>frontal theta</td>
<td>21% (0.093)</td>
<td>24% (0.103)</td>
</tr>
<tr>
<td>temporal theta</td>
<td>17% (0.078)</td>
<td>20% (0.079)</td>
</tr>
<tr>
<td>centroparietal theta</td>
<td>18% (0.087)</td>
<td>23% (0.096)</td>
</tr>
<tr>
<td>occipital theta</td>
<td>14% (0.086)</td>
<td>17% (0.071)</td>
</tr>
<tr>
<td>frontal alpha</td>
<td>42% (0.156)</td>
<td>37% (0.130)</td>
</tr>
<tr>
<td>temporal alpha</td>
<td>45% (0.138)</td>
<td>43% (0.092)</td>
</tr>
<tr>
<td>centroparietal alpha</td>
<td>46% (0.155)</td>
<td>44% (0.107)</td>
</tr>
<tr>
<td>occipital alpha</td>
<td>56% (0.171)</td>
<td>56% (0.111)</td>
</tr>
<tr>
<td>frontal beta</td>
<td>24% (0.110)</td>
<td>26% (0.132)</td>
</tr>
<tr>
<td>temporal beta</td>
<td>27% (0.122)</td>
<td>25% (0.093)</td>
</tr>
<tr>
<td>centroparietal beta</td>
<td>26% (0.124)</td>
<td>22% (0.089)</td>
</tr>
<tr>
<td>occipital beta</td>
<td>20% (0.120)</td>
<td>17% (0.085)</td>
</tr>
</tbody>
</table>
Mean frequency of region

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal</td>
<td>9.965 (1.210)</td>
<td>10.014 (1.549)</td>
<td>0.914</td>
</tr>
<tr>
<td>temporal</td>
<td>10.404 (1.321)</td>
<td>9.981 (1.095)</td>
<td>0.273</td>
</tr>
<tr>
<td>centroparietal</td>
<td>10.199 (1.359)</td>
<td>9.595 (1.099)</td>
<td>0.127</td>
</tr>
<tr>
<td>occipital</td>
<td>9.984 (1.239)</td>
<td>9.421 (0.958)</td>
<td>0.111</td>
</tr>
</tbody>
</table>

P300 evoked response

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Mean (SD)</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>latency, ms</td>
<td>374.392 (42.481)</td>
<td>385.554 (43.407)</td>
<td>0.453</td>
</tr>
<tr>
<td>amplitude, μV</td>
<td>7.910 (5.124)</td>
<td>4.986 (2.987)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Data given as mean and SD. In the hypothermia group, data are from 25 subjects; in the normothermia group, from 16 (Q-EEG), from 14 (P300 amplitude), or from 13 subjects (P300 latency).

No consistent correlations appeared between single Q-EEG parameter values and cognitive performance. Q-EEG or P300 variable values did not correlate with 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: the 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 two of the four measures of executive functioning: Stroop Interference task (r=0.53, p=0.0001) and Verbal Fluency task (r=0.44, p=0.004); and with two of the five tasks measuring learning and memory: fifth 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, a correlation between P300 latency and cognitive performance appeared in all but one test 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 one task of learning and memory: delayed retrieval of the AVLT (r=-0.37, p=0.009).

5.2.11 Prognostic factors for outcome

The following variables were chosen for the multivariate analysis, based on univariate analysis results or on previously established position as a risk factor for poor outcome after CA: treatment group, ROSC delay, age (categorized as under or over 65 years), trend in serum NSE levels (categorized as decreasing or increasing), occurrence of VTs during the first 2 days (categorized as absent or present), EF on the second-day TTE (categorized as below or over 35%), and etiology of the CA (categorized as ischemic or non-ischemic). The HRV variable chosen for the multivariate analysis was SDNN of the 24- to 48-hour recording (categorized as below
or over 100 ms (Task Force for the European Society of Cardiology and North American Society of Pacing and Electrophysiology 1996)), based on univariate analysis results (p=0.013 for association with good outcome in the hypothermia-treated group).

In multivariate analysis, the only variable associated with mortality was the ROSC delay (p=0.006). The variable predicting good outcome was short ROSC delay (p=0.011), but SDNN over 100 ms showed a nearly significant association (p=0.078). Because SDNN differed very significantly between treatment groups (p<0.001), a combined variable of the categorized SDNN and treatment group was entered into the model. In the model with this combined variable, SDNN over 100ms in the hypothermia-treated group was associated with good outcome (p=0.030), suggesting that this interaction does exist.
6 DISCUSSION

6.1 HACA trial

Induced hypothermia of 32 to 34ºC for 24 hours enhanced chances of survival and favorable neurological outcome in comatose CA patients resuscitated from VF or non-perfusing VT. Systemic external cooling was feasible, but slow for reaching the target temperature. The proportions of patients with any complication did not differ significantly between treatment groups, although a trend appeared toward a higher rate of infectious complications in the hypothermia-treated group.

This study has some limitations. Not all patients assigned to normothermia were normothermic during the first 48 hours, as the mean temperature in this treatment group during 32 to 48 hours after ROSC was nearly 38ºC. Elevated temperature worsens injury after global and focal ischemia in experimental models, and in humans elevated temperature after CA is associated with poor neurological outcome (Zeiner et al 2001). In that same study, risk for an unfavorable neurologic recovery increased with an OR of 2.26 (95% CI 1.24–4.12) for each degree Celsius higher than 37ºC. Thus in the HACA trial, hyperthermia may have worsened the outcome of patients assigned to normothermia. A tendency towards hyperthermia was also noted in hypothermia-treated patients after the warming period, as an overshoot phenomenon. In some patients, hyperthermia was probably related to aspiration pneumonia, common after resuscitation. The attending physicians could not be blinded to patient treatment assignment, which may have influenced the complication reporting. The HACA protocol did not provide defined criteria for selected complications, and among participating centers, the threshold for reporting a complication may have differed. Finally, the inclusion and exclusion criteria were strict, and these patients represent only a minor proportion of all resuscitated CA patients. Thus our results cannot be applied to all resuscitated patients.

6.2 Feasibility of therapeutic hypothermia in Helsinki

In our subjects, the delay from ROSC to achieving the target temperature (core temperature below 34.0ºC) was rather long, nearly 8 hours (mean 7 hours and 40 minutes). The same figure for the whole HACA trial was
also 8 hours. Most of our patients were hypothermic on admission to the emergency room (median tympanic temperature 35.3°C), but their temperature rose before they could be transferred to the ICU.

We used ice packs to enhance cooling, and the target temperature was reached in all our patients randomized to the hypothermia treatment. Surface cooling is, however, less effective than endovascular cooling. With endovascular cooling, the cooling rate has been reported to be 1.2°C per hour (Holzer et al 2006). In one rapid method of induction of hypothermia, Bernard et al gave their comatose CA survivors an i.v. infusion of 30 mL/kg ice-cold (4°C) lactated Ringer’s solution during 30 minutes. This resulted in a rapid decrease in core temperature with a cooling rate of 3.4°C per hour (Bernard et al 2003). Combining infusion of cold saline with endovascular cooling is a rapid method of achieving a core temperature of 33°C (Kliegel et al 2005). In the recently published Hypothermia After Cardiac Arrest Registry data, the median cooling rate was 1.1°C per hour (Arrich et al 2007).

In our study, therapeutic hypothermia was well tolerated. The most common adverse events in the hypothermia-treated patients during the first 7 days were pneumonia (75%) and bleeding of any severity (39%); in the whole HACA trial these were reported in 37% and 26% of their hypothermia groups (The Hypothermia After Cardiac Arrest study group 2002). The differences in pneumonia rates are most likely related to our practice of carefully reporting minor adverse events, as well, because the HACA protocol did not define criteria for diagnosis of pneumonia. Occurrence of sepsis in our hypothermia-treated patients was comparable to that of the whole HACA trial (6% vs 13%). The differences in bleeding rates may also be related to our low threshold of reporting any bleeding event, but may also be related to the difference in thrombolytic therapy. Of our hypothermia-treated patients, 36% received thrombolysis, whereas the respective number was 20% in the whole HACA trial. Only one patient in our study had clinically significant bleeding. Bernard et al reported no clinically significant hemorrhagic complications in CA patients treated with hypothermia (Bernard et al 2002). These results are in accordance with a recent report on the outcome of 50 patients resuscitated from out-of-hospital CA and treated with thrombolysis or PCI or both before therapeutic hypothermia. In that report, PCI was performed on 36 patients, and 11 patients received thrombolysis. No serious bleeding was observable in any patients (Hovdenes et al 2007). The article based on the Hypothermia After Cardiac Arrest Registry data reported that 3% (N=15) of all hypothermia-treated patients (N=462) had an episode of hemorrhage within 7 days after cooling, with specific treatment needed in only six cases (Arrich et al 2007).
6.3 Patient outcome in Helsinki

Our patients showed a trend towards better neurological outcomes with therapeutic hypothermia. Previous diabetes and severe hypocapnia on arrival at the emergency room were, however, slightly more common in patients assigned to normothermia, which may have had a negative effect on their outcomes. On the other hand, the cardiac enzyme levels on admission to the ICU and thereafter throughout the early study period were higher in patients randomized to hypothermia treatment, indicating their more pronounced ischemic damage.

Both our hypothermia and normothermia groups had higher rates for favorable outcome (69% and 47%) than did those reported in the entire HACA study of 2002 (55% and 39%) or by Bernard et al 2002 (49% and 26%). There are some possible explanations for this tendency. First, the EMS in the Helsinki region is of first-class quality, and the outcome rates of patients resuscitated from out-of-hospital VF CA were very good even before the use of therapeutic hypothermia (Roine et al 1990, Kuisma and Määttä 1996). This is in part reflected by the fact that the median time from collapse to ROSC was shorter for our patients than those reported in the HACA study: 18 minutes (hypothermia) and 18.5 minutes (normothermia) versus 21 and 22 minutes. Moreover, the percentage of patients receiving bystander-initiated CPR was slightly higher in our study population than in the HACA trial: 50% (hypothermia group) and 56% (normothermia group) versus 43% and 49%. To our knowledge, Helsinki had the best overall outcome rates among the nine centers of the HACA study. The slightly greater difference in good outcome between the two treatment groups is most likely related to the relatively small number of patients in our study.

The cause of death in our patients was neurological in two-thirds of the cases. This is in accordance with a previous study (Laver et al 2004), which did not include hypothermia-treated patients. Ploj et al have presented a preliminary report based on 21 deaths in a cohort of 49 VF CA patients treated with hypothermia. Their study suggests that mild induced hypothermia does not change the mode of death in out-of-hospital CA patients resuscitated from VF (Ploj et al 2006, abstract).

6.4 Serum markers of neuronal injury

Hypothermia resulted in decreasing levels of serum NSE, reflecting amelioration of secondary ischemic neuronal injury. The serum levels of NSE significantly differed between hypothermic and normothermic patients. The decrease in serum NSE values after CA was associated with recovery of consciousness, with good neurological outcome, and with
survival for at least 6 months, whereas increasing levels of serum NSE were associated with poor outcome. These results suggest that the time-course of serum NSE between 24 and 48 hours after CA may be helpful in clinical decision-making.

The time-course of serum S-100B protein between 24 and 48 hours after CA did not differ between the hypothermia- and normothermia-treated groups, nor was it associated with clinical outcome. This may, however, be related to the chosen time-points in the serum sampling, since a study by Hachimi-Idrissi et al showed a significant decrease in serum S-100B levels between admission and 24 hours after CA in their hypothermia-treated group (Hachimi-Idrissi et al 2005). Decreasing levels of serum NSE but not of S-100B over time may indicate selective attenuation of delayed neuronal death by therapeutic hypothermia. Neurons are more sensitive to hypoxic injury than are astrocytes. A selective increase in NSE but not in S-100B over time in CSF has been reported in children with inflicted traumatic brain injury (Berger et al 2002).

In our study, patients treated with hypothermia achieved a good recovery (CPC 1 or 2) with significantly higher NSE levels measured at 24 hours after CA than those of patients with a good outcome in the normothermia group. This may reflect the ability of hypothermia to provide cerebral protection despite initial neuronal damage, preventing continuing injury and release of these ischemia markers into the blood stream. Furthermore, ROC analysis of serum NSE and S-100B at different time-points revealed that cut-off values predicting unfavorable outcome with a specificity of at least 95% were higher in the hypothermia group. The sensitivity of these tests was notably poor in the hypothermia group, however. Thus the use of hypothermia may reduce the prognostic value of both serum NSE and S-100B in outcome prediction.

Previous studies on normothermic CA patients have suggested similar (Fogel et al 1997, Schoerkhuber et al 1999, Meynaar et al 2003) or lower (Martens et al 1998) cut-off values for serum NSE, compared to our cut-off values assessed by ROC analysis for hypothermic patients. In our normothermic patients, cut-off values were only slightly elevated or fell within the reference range for serum NSE. The recently published recommendations of the American Academy of Neurology state that serum NSE > 33 μg/L at days 1 to 3 after CPR accurately predict poor outcome (Wijdicks et al 2006). This has been challenged by Reisinger et al who reported, in their study population of 177 CA patients, nine patients with grade CPC 1 or 2 recovery and serum NSE-levels exceeding 33 μg/L (Reisinger et al 2007). They found that a peak serum NSE concentration exceeding 80 μg/L predicted permanent coma with a specificity of 100%. The recommendation of the American Academy of Neurology is based on studies that have not used therapeutic hypothermia. In the study of Reisinger et al, only 11% of patients had undergone therapeutic
hypothermia. They found no significant difference in any measure of diagnostic accuracy between patients treated with hypothermia (N=20) and those not undergoing this treatment (N=157), but their small number of hypothermia-treated patients limits the possibility of detecting such a difference (Reisinger et al 2007). Data on NSE levels in hypothermia-treated CA patients is thus still very limited.

Since the level of NSE was not measured from CSF in our study, evidence on the effect of therapeutic hypothermia remains elusive. However, a high correlation between serum and CSF NSE values has been reported (Roine et al 1989, Martens et al 1998). The advantage of serum biomarkers is the ease of data acquisition. Repeated lumbar punctures are inconvenient in ICU settings and may even be contraindicated due to induced thrombolysis or elevated ICP. It cannot be entirely excluded that the decrease in serum NSE levels seen in patients assigned to hypothermia is related to a reduction in cerebral blood flow caused by hypothermia. However, the hypothermia lasted 24 hours, and with this assumption one would expect to see a rise in NSE levels at 48 hours.

6.5 Evoked potentials

SEP and BAEP recordings are non-invasive, reproducible techniques easily performed at bedside in the ICU. Induced hypothermia requires muscle relaxation, which prevents adjustment of SEP stimuli intensity based on thumb twitch. In these patients, the intensity of the stimuli has to be sufficient to evoke an ipsilateral supraclavicular response. In our study, the bilateral absence of early N20 cortical responses was a reliable predictor of permanent coma after CA also in patients treated with therapeutic hypothermia of 33ºC. However, the presence of N20 responses did not indicate recovery of consciousness. The power of this study was not sufficient to detect a possible correlation between outcome and N20 peak latencies or between outcome and N20 amplitudes. In normothermic CA survivors, hypoxic-ischemic brain damage with poor outcome is associated with prolonged latencies and decreased amplitudes of SEP N20 peaks (Bauer et al 2003).

At a core temperature of 33ºC, the N20 response appears approximately 24 ms after the stimulus. The increase in N20 response latency in the hypothermia-treated group was expected, as hypothermia significantly reduces nerve conduction velocities and lengthens cervicocortical conduction time. This reflects a slowing of neural conduction along the axons and an increase in synaptic delay (Benita and Conde 1972). Amplitudes of N20 responses did not differ between the two treatment groups, which is in concordance with the study of Porkkala et al (Porkkala et al 1997).
BAEP recordings did not prove useful in identifying CA patients with poor prognosis, either when used alone or in combination with short-latency SEPs. Missing waveforms in BAEP can indicate a lesion in the brain stem, but this finding may also be attributed to hearing loss, which is a common confounding factor, especially in elderly patients.

6.6 Arrhythmias and HRV

Risk for recurrent arrhythmias is significantly increased after CA and resuscitation (van Alem et al 2003). Hypothermia is also associated with cardiac arrhythmias: A higher number of arrhythmias has been reported in accidental hypothermia (White 1984), and postoperative VT occurs more frequently in patients with coronary artery disease who are mildly hypothermic (35°C) during major surgery (Frank et al 1997). This arrhythmogenic propensity contradicts findings in experimental studies in which regional hypothermia has preserved ischemic cardiac tissue by reducing myocardial oxygen demand (Hale and Kloner 1997) and by improving cardiac energy metabolism (Simkhovich et al 2004).

We found slight differences in the occurrence of ventricular arrhythmias between groups. The number of VTs did not differ, but the number of PVBs was higher among the hypothermia-treated patients. Levels of cardiac enzymes were higher in patients randomized to hypothermia treatment even on admission to ICU and thereafter throughout the early study period, indicating larger-sized infarcts in this group, which possibly in part explains this finding. Although three hypothermia-treated patients had recurrent VF during the first 48 hours after CA, as compared to one in the normothermia group, only one of these VF episodes occurred during the actual hypothermia. In conclusion, mild therapeutic hypothermia after CA had a neutral effect on the occurrence of clinically significant cardiac arrhythmias.

The equal distribution of clinically significant ventricular tachyarrhythmias among treatment groups is in accordance with previous data. In the entire HACA study population, lethal or long-lasting arrhythmias were not significantly more frequent in hypothermia-treated patients, and the study of Bernard et al reported no clinically significant cardiac arrhythmias in such patients (The Hypothermia After Cardiac Arrest study group 2002, Bernard et al 2002). In a trial evaluating the feasibility of endovascular cooling to 33°C as an adjunct to primary percutaneous coronary intervention for acute MI, ventricular arrhythmias requiring cardioversion occurred in 14% of patients in the cooling group and in 29% of controls (Dixon et al 2002). The study of Holzer et al evaluating the safety of endovascular cooling after CA reported a significant increase in transient bradycardia, but not in tachyarrhythmias between admission
and 32 hours after CA (Holzer et al 2006). Boddicker et al have reported that existing hypothermia actually improves both defibrillation success and resuscitation outcomes from induced VF in swine, and in that study, outcomes were best in the group with hypothermia of 33°C (Boddicker et al 2005). In the HACA Registry data, 6% of hypothermia-treated patients experienced at least one episode of arrhythmia within 7 days after cooling (Arrich et al 2007).

HRV reflects neural control of the heart rhythm. Although its physiological background is not fully understood, it has been used in the evaluation of neurocardiogenic interaction as a part of risk stratification in patients with various heart diseases. HRV evaluated from 24-hour ECG provides prognostic information in patients with MI or cardiac failure. Loss of HRV after MI is associated with increased mortality (Kleiger et al 1987), and HRV analysis has been used for risk stratification after MI. Reduced long-range HRV among patients with chronic heart failure is also associated with increased mortality (Nolan et al 1998). HRV is reduced in patients resuscitated from CA, and also from CA not associated with coronary artery disease, and it may identify patients who will die within one year after CA (Huikuri et al 1992, Fei et al 1994, Dougherty and Burr 1992). It has been suggested that real-time analysis of HRV in critical illness might provide additional information about patient status and prognosis (Buchman et al 2002, Gang and Malik 2002). Reduced HRV values predict mortality in patients with multiple organ dysfunction syndrome (Schmidt et al 2005) and after trauma (Grogan et al 2004).

In our study, all HRV values were significantly higher in the hypothermia group in the 0- to 24-hour recording than in normothermic controls, suggesting preserved autonomic modulation of the heart and a favorable effect of hypothermia. This effect was carried through the 24- to 48-hour recording. At 14 days no differences emerged between the treatment groups, but most of the patients with poor outcome had already died.

Several possible explanations exist for the higher HRV values in the hypothermia group. First, HRV is inversely associated with heart rate, and the increased HRV during hypothermia may therefore be a physiological phenomenon related to bradycardia (Kleiger et al 1987). Second, there may also occur a true temperature-induced change in autonomic nervous activity, which then increases the HRV. MacKenzie et al reported that four patients with severe thermolability (but no cardiovascular diseases) showed significantly enhanced HRV during steady hypothermia (33.9 ± 0.7°C), as compared with normothermia (MacKenzie et al 1992). The association of decreased temperature and increased HRV has also been shown in isolated rat hearts (Langer et al 1999). The variability of interbeat intervals in that study was always greater during hypothermia than for the same heart rate induced pharmacologically.

Third, increased HRV may reflect the beneficial effect of hypothermia
on myocardial function. Cold cardioplegia and topical cooling have been used to protect the heart from ischemic injury during cardiopulmonary bypass surgery. Mild core hypothermia in awake healthy human subjects is associated with increased myocardial perfusion (Frank et al 2003). Although ischemic myocardial damage was already more pronounced in our hypothermia patients – as demonstrated by their serum cardiac enzyme levels on admission to ICU – the echocardiograms recorded during the cooling period showed no difference in myocardial function.

Lastly, improved HRV may be related to neuroprotection resulting from hypothermia. Impaired cerebral function as a consequence of severe traumatic brain injury has been associated with decreased HRV and poor outcome (Lowensohn and Weiss 1977, Leipzig and Lowensohn 1986, Haji-Michael et al 2000). HRV is reduced in patients with ischemic stroke, and abnormal heart rate dynamics have been identified as a prognostic marker for post-stroke mortality (Korpelainen et al 1996, Mäkikallio et al 2004). In univariate analysis, the HRV variables with predictive value were all from the 24- to 48-hour recording. A higher HRV at this time-point may reflect more efficient autonomic control, with more responsiveness to the external stimuli emerging, as sedative medication is decreased. In a pilot study examining serial HRV measurements in brain-trauma patients, decreased HRV in the awakening period was associated with worsened cerebral disorders (Rapenne et al 2001).

There are several limitations to this study. The ECG recordings of patients assigned to hypothermia reflect arrhythmias and HRV under changing temperature conditions, as these patients were first cooled during the 0- to 24-hour recording and then rewarmed during the 24- to 48-hour recording. This complicates interpretation of the HRV results. Most our patients received beta blockers during the first 48 hours, which may have increased their HRV and diminished its predictive value. However, LF and SDNN have been reported to preserve their predictive ability during beta blockade (Niemelä et al 1994, Tapanainen et al 2002). The patients also received pancuronium, which has an atropine-like effect on heart rate. However, in most cases HRV is reduced, and pancuronium was used in both treatment groups. Long-range HRV indexes are in part dependent on range of daily activity, and level of activity can thus be a confounding factor at the 14-day recording (Roach et al 2004). During the first two Holter recordings, all of our patients were immobilized, excluding the effect of physical activity. No previous reports exist on the ability of early HRV measurements to predict outcome after CA. However, HRV assessed early after acute MI has predicted short-term mortality and major complications (Carpeggiani et al 2004).

Our results suggest that hypothermia may preserve autonomic regulation of the heart. The mechanism of action remains unclear, however. We hypothesize that the preserved HRV may be both a reflection of
neuroprotection and a direct effect of hypothermia on heart rate. Preserved HRV was associated with a more favorable outcome in hypothermia-treated patients.

6.7 Cognitive and neurophysiological outcome

Of those hypothermia-treated, 67%, and of normothermia-treated patients, 44% were cognitively intact or had only subtle deficits at 3 months after CA. Severe cognitive deficits were detected in 15% of the hypothermia-treated and in 28% of the normothermia-treated group. Although a trend appeared toward better cognitive outcome in the hypothermia group, the differences were not significant. A total of 33% of patients had deficits in executive functioning, 24% in learning and memory, and 19% in speed of performance.

When compared figures reported earlier (Roine et al 1993b, van Alem et al 2004a), the proportion of cognitively intact patients in our study was slightly higher in the hypothermia-treated group and similar in the normothermia-treated group. However, in the study of van Alem et al, the time-point for neuropsychological evaluation was 6 months. We selected the 3-month time-point to exclude the habituation effect, because neuropsychological rehabilitation for selected patients was not started until after this time-point.

In our study, the most commonly impaired cognitive domain was executive functioning, followed by memory and learning. This has not been reported in previous studies, and can be explained by the fact that those groups studied memory functions more extensively than they studied executive functions. Grubb et al reported a correlation between resuscitation delays and memory impairment (Grubb et al 1996), van Alem et al reported only a weak correlation between resuscitation delays and cognition, and Roine et al did not detect any such correlation (van Alem et al 2004a, Roine et al 1993b). In our study, cognition did not correlate with resuscitation delays. Instead, most of the cognitive variables measured correlated with P300 response and with CPC outcome.

It is important to recognize that cognitive impairment is not uncommon after survival from a critical illness. A recent study examining cognitive performance and specifically executive function in a population of general intensive care survivors found that at 3 months after discharge from ICU, these functions were very significantly impaired in 35% (Sukantarat 2005).

We saw a trend for better outcomes in the hypothermia-treated group as measured by Q-EEG, but these differences did not reach the level of significance. The amplitude of the P-300 response was significantly higher in the hypothermia-treated group. In patients with cognitive impairment,
the latency of this response is increased, and the amplitude of the response is lower (Picton 1992). None of the Q-EEG variables nor the latency nor amplitude of the P300 response correlated with resuscitation delays. Instead, the latency and amplitude of the P300 response correlated with most of the cognitive variables measured. This absence of any association between resuscitation delays and neuropsychological and neurophysiological test results may in part occur because most of our patients achieved a good outcome.

6.8 Prediction of outcome

In multivariate analysis, the only variable predicting mortality was ROSC delay. Variables associated with good neurological outcome were short ROSC delay and in the hypothermia-treatment group, SDNN over 100 ms on the second-day ambulatory ECG recording. The relatively small sample size limits interpretation of the multivariate analysis results. There occurred an interaction between preserved HRV and good neurological outcome in the hypothermia-treated group, but further studies are warranted to assess whether preserved HRV is a true predictive factor for good neurological outcome.

The use of therapeutic hypothermia is a challenge for early prognostication. Prediction methods developed on normothermic patients should not be applied to patients treated with hypothermia without further validation studies. Clinical status is of less importance with the use of therapeutic hypothermia, because induced hypothermia requires muscle relaxation, sedation, and mechanical ventilation. The predictive value of absent or present brain stem reflexes or motor response in comatose CA patients treated with hypothermia remain to be studied. Sedation and analgesia severely interfere with neurological evaluation, and the possible effect of individual medications on clinical status should always be carefully considered. Additionally, hypothermia may prolong the effects of anesthetic agents (Sessler 2001, Fukuoka et al 2004). Prognostic evaluation is not recommended during hypothermia or shortly after rewarming the patient.

No generally accepted cut-off values for single serum biomarkers exist that predict poor outcome with 100% specificity and reasonable sensitivity. Instead of a single assessment of a serum marker, serial determinations of serum biomarkers may provide information on the evolution of neuronal damage (Schoerkhuber et al 1999, Prohl et al 2007). Our results suggest that the time-course of serum NSE between 24 and 48 hours after CA may help in clinical decision-making. However, use of therapeutic hypothermia seems to reduce the prognostic value of both serum NSE and S-100B in outcome prediction. Thus far, only the bilateral absence of early cortical responses
in median nerve SEPs can be generally considered an accurate predictor of permanent coma after CA, and this is true also in hypothermia-treated patients. Unfortunately, this method lacks sensitivity in identifying patients who will have poor outcome. The presence of cortical responses in SEP recording does not guarantee recovery of consciousness. The finding that continuous aEEG at normothermia after 24 hours of induced hypothermia predicts recovery of consciousness is very promising (Rundgren et al 2006). Although the majority of patients regaining consciousness eventually achieve a good outcome, recovery of consciousness does not necessarily imply a good neurological outcome. Unfortunately, no methods are yet available to predict good outcome accurately. Our study suggests that preserved HRV on the second day after CA may be associated with good outcome. These preliminary results should be confirmed in a larger study.

A multimodality approach in predicting outcome early after CA has been recommended in several recent studies (Meynaar et al 2003, Pfeifer et al 2005, Prohl et al 2007). These studies have combined biochemical markers with SEP (Meynaar et al 2003, Prohl et al 2007) or clinical investigation or both (Pfeifer et al 2005, Prohl et al 2007). The predictor indexes suggested by these studies still need to be validated in prospective studies.

The relatively small sample size in our own studies limits the interpretation of these results. It also causes the analyses to be disposed to possible type II error. However, over 3 years of a doctor’s being constantly on call was necessary for collecting this patient population. The number of study patients was limited to those involved in the HACA study, and limited funding and resources did not allow extension of that trial. Due to the strict inclusion and exclusion criteria, these patients represent only a minor proportion of all resuscitated CA patients; thus the results cannot be applied to all resuscitated patients treated with hypothermia. Still, VF CA patients are the group in which studies have shown therapeutic hypothermia to be effective in ameliorating neurological outcome.

As the amount of evidence and the number of studies concerning outcome prediction in hypothermia-treated patients are still limited, caution and discretion are required in assessing the neurological prognosis for these patients, particularly regarding end-of-life decisions.
7 CONCLUSIONS

Lowering the body temperature to 33°C for 24 hours resulted in improved neurological outcome and survival after out-of-hospital VF CA arrest. The complication rate did not differ significantly between hypothermia- and normothermia-treated patients (Study I).

Therapeutic hypothermia was associated with a trend toward a decrease in serum NSE levels, a decrease which was less common in normothermic patients. This may reflect less damage to the cerebral blood-brain barrier and reflect the neuroprotective effect of hypothermia. Use of therapeutic hypothermia seems, however, to reduce the prognostic value of both serum NSE and S-100B in outcome prediction (Study II).

The prognostic ability of median nerve short-latency SEPs may not be affected by therapeutic hypothermia. The bilateral absence of early N20 cortical responses was a reliable predictor of permanent coma after CA in these patients. Recording of BAEPs provided no additional benefit for outcome prediction (Study III).

Mild therapeutic hypothermia had a neutral effect on occurrence of clinically significant cardiac arrhythmias. In the hypothermia group during the first 2 days, the mean heart rate was significantly lower, and number of isolated PVBs, bigeminy, and couplets was increased. Numbers of VTs or VF s between treatment groups did not differ. At 14 days after CA, no significant differences emerged in any Holter variables between the groups. All HRV values were significantly higher in the hypothermia group in the 0- to 24-hour recording than in normothermic controls, suggesting preserved autonomic modulation of the heart and a favorable effect from hypothermia. The mechanism behind the HRV response remains unsettled, but we hypothesize that the preserved HRV may be secondary to neuroprotection in combination with the direct effect of hypothermia on heart rate regulation (Study IV).

Therapeutic hypothermia of 33°C for 24 hours after out-of-hospital VF CA was associated neither with cognitive decline nor with neurophysiological deficits: 67% of the survivors in the hypothermia group and 44% in the normothermia group were cognitively intact or had only subtle cognitive deficits. The most commonly impaired cognitive domain was executive functioning, followed by memory and learning.
The increased survival with hypothermia treatment was not associated with any increase in survivors with clinically significant cognitive deficits. The neurophysiological outcome, measured by P-300 and Q-EEG, was at least as good in the hypothermia-treated group as after traditional care. No significant differences existed in Q-EEG parameters between treatment groups. The amplitude of the P-300 response was significantly higher in the hypothermia-treated group (Study V).

Early prediction of outcome in hypothermia-treated CA patients is challenging. Most of the patients achieving a good outcome did not recover consciousness during the first 48 hours. Short ROSC delay was associated with good neurological outcome and survival. Bilaterally absent cortical N20 responses in SEP recorded as early as 24 to 28 hours after CA accurately predicted persistent coma, but this method detects only some of the patients with poor outcome. Cut-off values for serum NSE and S-100B predicting poor outcome with a specificity of at least 95% had remarkably poor sensitivity. Prognostic evaluation in hypothermia-treated patients should not be undertaken during hypothermia or shortly after rewarming the patient. A multimodality approach to prediction of outcome is recommended: Clinical status, time-trend of the NSE-levels, and early cortical responses of SEP. The number of studies concerning outcome prediction in hypothermia-treated patients is still limited, and caution is needed in assessing the neurological prognoses in these patients. Clinical decisions leading potentially to withdrawal-of-treatment decisions should not depend on a single marker but be based on all available prognostic information.
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Marjaana Tiainen
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