Arrhythmias and heart rate variability during and after therapeutic hypothermia for cardiac arrest*

Marjaana Tiainen, MD, PhD; Hannu J. Parikka, MD, PhD; Markku A. Mäkijärvi, MD, PhD; Olli S. Takkunen, MD, PhD; Seppo J. Sarna, PhD; Risto O. Roine, MD, PhD

Objective: **To evaluate the effects of therapeutic hypothermia (HT) of 33°C after cardiac arrest (CA) on cardiac arrhythmias, heart rate variability (HRV), and their prognostic value.**

Design: **Prospective, comparative substudy of a randomized controlled trial of mild HT after out-of-hospital CA, the European Hypothermia After Cardiac Arrest study.**

Setting: **Intensive care unit of a tertiary referral hospital (Helsinki University Hospital).**

Patients: **Seventy consecutive adult patients resuscitated from out-of-hospital ventricular fibrillation were randomly assigned either to therapeutic HT of 33°C or normothermia.**

Interventions: **Patients randomized to HT were cooled with an external cooling device for 24 hours and then allowed to rewarm slowly during 12 hours. In the normothermia group, the core temperature was kept <38°C by antipyretics and physical means. All patients received standard intensive care for at least 2 days.**

Measurements and Main Results: **Twenty-four hour ambulatory electrocardiography recordings were performed at 0–24 hours, at 24–48 hours, and at 14 days. The clinical outcome was assessed at 6 months after CA. The occurrence of premature ventricular beats was increased in the HT-treated group during the first two recordings, with no difference in the number of ventricular tachycardia or ventricular fibrillation episodes. All HRV values were significantly higher during the HT ($p < 0.01$), but no differences were observed 2 weeks later. In multivariate analysis, only shorter delay to restoration of spontaneous circulation ($p = 0.009$) and the SD of individual normal-to-normal intervals >100 msec of the 24–48-hour recording in the HT group ($p = 0.018$) predicted good outcome.**

Conclusions: **The use of therapeutic HT of 33°C for 24 hours after CA was not associated with an increase in clinically significant arrhythmias. Preserved 24 to 48-hour HRV may be a predictor of favorable outcome in patients with CA treated with HT. (Crit Care Med 2009; 37:403–409)**

KEY WORDS: cardiac arrest; hypothermia; tachyarrhythmias; heart rate variability; prognosis

Mild hypothermia (HT) of 33°C for 12 or 24 hours improves neurologic outcome and survival after out-of-hospital ventricular fibrillation (VF) cardiac arrest (CA) (1, 2). The risk of recurrent arrhythmias is known to be significantly increased after CA and resuscitation (3). The effects of therapeutic HT on cardiac electrical activity after CA are not yet fully known. An increased number of arrhythmias have been reported in accidental HT (4). Postoperative ventricular tachycardia (VT) occurs more frequently in patients with coronary artery disease, who are mildly hypothermic (35°C) during major surgery (5). This arrhythmogenic propensity contradicts findings in experimental studies, where regional HT has preserved ischemic cardiac tissue by reducing myocardial oxygen demand (6) and by improving cardiac energy metabolism (7). To our knowledge, no studies reporting results of 24-hour ambulatory electrocardiography (ECG) recordings performed on patients with CA early after the resuscitation have been published, and there is need for cardiac safety data concerning therapeutic HT after CA.

Heart rate variability (HRV) evaluates beat-to-beat fluctuations in the heart rate during sinus rhythm. These variations are considered to rise 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 (8). Although its physiologic background is not fully understood, HRV has been used in the evaluation of neurocardiac interaction as part of risk stratification in patients with various heart diseases. 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 (8). HRV evaluated from 24-hour ECG provides prognostic information in patients with myocardial infarction (MI) or cardiac failure. Loss of HRV after MI is associated with increased mortality (9), 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 (10). HRV is reduced in patients resuscitated from CA, also in CA not associated with coronary artery disease, and it may differentiate patients who will die within 1 year after CA (11–13). It has been suggested that real-time analysis of HRV in critical ill-

*See also p. 735.

From the Departments of Neurology (MT, ROR), Cardiology (HJP, MAM), Anesthesiology and Intensive Care Medicine (OST), and Public Health (SJS), Helsinki University Hospital; and Department of Neurology (ROR), Turku University Hospital, Finland.

This study was performed at the Intensive Care Unit of Helsinki University Hospital, Haartmaninkatu 4, 00029 HUS, Finland.

Supported, in part, by the Finnish Neurology Foundation, Maire Taponen Foundation, Laerdal Foundation, Research Foundation of Orion Corporation, and Helsinki University Hospital. Kinetic Concepts Inc., Wareham, UK provided the cooling device used in this study.

The authors have not disclosed any potential conflicts of interest.

For information regarding this article, E-mail: marjaana.tiainen@hus.fi

DOI: 10.1097/CCM.0b013e31819572c4

ness might provide additional information about patient status and prognosis (14, 15). Reduced HRV values predict mortality in patients with multiple organ dysfunction syndrome (16) and after trauma (17). Furthermore, impaired cerebral function as a consequence of severe traumatic brain injury has been associated with decreased HRV and poor outcome (18–20). HRV is reduced in patients with ischemic stroke, and abnormal heart rate dynamics have been identified as a prognostic marker for poststroke mortality (21, 22). The effects of therapeutic HT on HRV and its predictive value are currently unknown.

The aim of this study was to examine the effects of therapeutic HT of 33°C after CA on cardiac arrhythmias and HRV and to evaluate their prognostic value.

SUBJECTS AND METHODS

The ethics committee of Helsinki University Hospital approved the protocol and consent procedure of this study in accordance with institutional guidelines. A deferred consent was used for all patients. The patient's family was informed about the trial as soon as they were reached, and they had the possibility to withdraw the patient any time from the study. Information about the study was provided to all patients as soon as they were able to receive this information.

Patients randomized into the Hypothermia After Cardiac Arrest trial were included (1). All adult patients admitted to the Helsinki University Hospital after resuscitation from out-of-hospital CA were screened for the trial. The inclusion criteria were witnessed CA of presumed cardiac origin with VF or nonperfusing VT as the initial rhythm, an age of 18–75 years and unconsciousness (Glasgow Coma Scale score <9). Patients responding to any verbal command after restoration of spontaneous circulation (ROSC) were excluded. Additional inclusion and exclusion criteria have been described previously (1).

All CA data were collected according to the Utstein style (23). CA was defined as the absence of both palpable pulse and spontaneous respiration. ROSC was defined as return of palpable arterial pulse. Basic and advanced cardiac life support were provided by the three-tiered Emergency Medical Services. Patients were transferred to the intensive care unit (ICU) after assessment of respiratory and hemodynamic function and initial neurologic evaluation in the emergency department. All patients received standard ICU management and monitoring as described previously (1).

Sedation and analgesia were accomplished using midazolam 0.125 $mg \cdot kg^{-1} \cdot hr^{-1}$ and fentanyl 0.002 $mg \cdot kg^{-1} \cdot hr^{-1}$ intravenously for 32 hours. To avoid shivering, pancuronium 0.05 $mg \cdot kg^{-1} \cdot hr^{-1}$ 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. Mean arterial pressure was targeted at 80 mm Hg. Inotropic drugs 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 the blood glucose concentration exceeded 10 mmol/L, targeting at normoglycemia. Optimal direct head-up-position (30°) was maintained.

Patients randomized to HT treatment were actively cooled externally with a surface cooling device (Therakool Kinetic Concepts, Wareham, UK) to a core temperature of 33°C ± 1°C. The cooling device delivers cold air over the entire body and into a mattress. HT was maintained for 24 hours from the start of cooling, and patients were then allowed to rewarm spontaneously over the next 12 hours. Those randomized to normothermia (NT) were allowed to rewarm passively and were then kept normothermic by physical and antipyretic means, if the core temperature exceeded 38°C. The temperature was measured from the urinary bladder by a Foley catheter with a temperature sensor. Life support was maintained for at least 3 days in all patients and at least for 7 days in patients responding to pain in any manner. Withdrawal of care meant withdrawal of inotropic intravenous medications but maintenance of airway and ventilator treatment.

Holter Recordings. Twenty-four hour ambulatory ECG recordings were performed with a portable two-channel tape recorder (Oxford Medilog, Oxford Medical, UK) three times during the first 2 weeks after CA. The first recording (referred as 0–24 hours) was started in the emergency room after randomization. The second recording was started immediately after the first recording (referred as 24–48 hours). The third recording was accomplished 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 was continued with decreased doses. All patients remained in supine head-up position (30°) during the first and second recordings. During the third recording, all patients were allowed normal physical activity. The tapes were analyzed by two observers independently and blinded to the treatment group and other clinical data. The total number of supraventricular premature beats per hour and the total number of premature ventricular beats (PVBs) per hour was calculated from Holter recordings. Three or more consecutive PVBs at a rate of >120 beats/min were classified as VT.

Measurement of Autonomic Regulation of the Heart. HRV was assessed by time domain and frequency domain methods from the 24-hour Holter recordings (8). For HRV calculations only normal sinus beat intervals were used. Fast Fourier transformation was used to separate the R-R fluctuations to frequencies. The spectral bands used were 0.15–0.40 Hz (high frequency), 0.04–0.15 Hz (low frequency, LF), and 0.01–0.40 Hz (total power). The spectral measures were computed as amplitudes, which are square roots of areas under the power spectrum, and are presented in milliseconds. The areas represent signal variance within frequency bands, whereas the square root represents the SD. The high frequency and LF components were determined from the entire 24-hour recording. LF power reflects sympathetic and parasympathetic modulations of heart rate, whereas high frequency power mainly reflects vagal modulation (8). The following variables were used as the time domain methods: the SD of individual normal-to-normal intervals (SDNN) and the SD of the averaged normal-to-normal intervals for all 5-minute periods of the 24-hour recording (SDANN). Both SDNN and SDANN reflect a mixture of sympathetic and parasympathetic modulation of heart rate, with other physiologic influence on heart rate as well. SDNN provides an estimate of the overall variability of HRV. The normal value for SDNN is 141 ± 39 msec (mean ± SD) and for SDANN 127 ± 35 msec (8). Severely decreased SDNN <50 msec is associated with increased mortality in patients with MI and in patients with chronic heart failure, when compared with SDNN >100 msec (9, 10).

Other Measurements. Blood was sampled for cardiac enzymes CK, CK-Mb, and troponin-T at admission to ICU, 24 and 48 hours after the start of cooling or at respective time points in NT group and on the third day after CA to study the changes in serum cardiac enzyme levels over time. Transthoracic echocardiogram (TTE) was performed to assess left ventricular systolic function at 24–30 hours after CA. The Simpson method was used to calculate ejection fraction (EF) (24). The HT-group patients were still hypothermic during the TTE. The patients were categorized into three groups by the TTE: EF <35%, EF 35% to 50%, and EF >50%. The cause of CA was classified as acute MI, myocardial ischemia without infarction, primary arrhythmia, or unknown by a cardiologist after reviewing all patients' data. MI and ischemia were defined according to the guidelines of the Joint European Society of Cardiology and American College of Cardiology Committee (25).

Assessment of Outcome. The outcome was assessed at 6 months after CA by the Pittsburgh Outcome Scale (23, 26). This is a five-category scale of cerebral performance categories (CPC). The categories are defined as follows: CPC 1, normal cerebral function; CPC 2, conscious with moderate cerebral function; CPC 3, conscious with severe cerebral disabil-

ity; CPC 4, comatose or in persistent vegetative state; and CPC 5, dead. The neurologic outcome was dichotomized into good (CPC 1 and 2) or poor (CPC 3, 4, and 5). The outcome was assessed on a follow-up visit by the same neurologist.

Statistical Analysis. Categorical variables are given as counts and percentages. Data are given as median and range. Continuous data were compared with the Mann-Whitney *U* test. The changes in serum cardiac enzyme levels over time were analyzed using two-way analysis of variance for repeated measures after logarithmic transformation. Outcome data are binary, and the chi-square test was used to compare proportions between HT and NT groups. Multivariate analysis was performed using a logistic regression model with good outcome at 6 months as the dependent variable. p values <0.05 were considered as statistically significant. The number of study patients was limited to patients involved in the Hypothermia After Cardiac Arrest study. According to *post hoc* sample-size analysis, this study had a power of 80% to detect a 30% change in the number of patients with at least one VT at a significance level of 0.05. Statistica data analysis software system (StatSoft, Tulsa, OK) and SPSS version 12.0 (SPSS, Chicago, IL) were used in data analysis.

RESULTS

Altogether 70 consecutive unconscious patients met the Hypothermia After Cardiac Arrest inclusion criteria and were randomly assigned to HT (n = 36) or NT (n = 34) treatment. Clinical and demographic data of patients are presented in Table 1. No significant differences were observed in the baseline characteristics or treatment options before the admission to the emergency department between the two treatment arms. There were no statistically significant differences in concomitant drug treatment between groups: 15 patients (42%) in HT and 9 patients (27%) in NT-treated group received at least one dose of antiarrhythmic medication in the ICU during the first 48 hours after ROSC ($p = 0.214$). In the HT group, 12 patients received lidocaine (three of them only a single bolus), two patients received amiodarone, and one patient received both lidocaine and amiodarone. In the NT group, eight patients received lidocaine, four patients received amiodarone, and one patient received adenosine. In HT-treated group, 31 patients (86%) and in NT-treated group 30 patients (88%) received inotropic drugs during the first 48 hours. Beta blockers were administered to 34 (94%) and 30 (88%) of the HT and NT patients during the first 48 hours, respectively. Only one patient (HT group) underwent acute percutaneous coronary intervention before the ICU treatment.

The etiology of CA in the HT and the NT groups was acute MI in 24 patients (67%) and in 21 patients (62%), ischemia in 5 (14%) and in 3 (9%), and primary arrhythmia in 7 (19%) and in 10 (29%), respectively.

The prerandomization serum levels of the cardiac enzymes were higher in the HT-assigned group at admission to the ICU (median: CK, 642 vs. 275 U/L; $p = 0.004$; CK-Mb, 31 vs. 10 μg/L; $p = 0.019$; troponin-T, 1.36 vs. 0.40 μg/L; $p = 0.048$) and remained higher during the entire study period. The changes in the serum CK and troponin-T levels over time did not differ between the two treatment groups ($p = 0.067$ and $p = 0.508$), but the CK-Mb values decreased more slowly in the HT-treated group ($p < 0.001$).

The EF at 24 hours after CA was <35% in nine of HT-treated (25%) and in ten of NT-treated patients (29%); 35% to 50% in 15 HT- (42%) and in 15 NT-group patients (44%); and >50% in ten HT-treated (28%) and in six NT-treated patients (18%). TTE could not be performed in five patients. The QRS duration measured from ECGs taken 2, 24, and 48 hours after CA did not differ between the two groups. New Q-waves on ECG evolved in seven HT-treated patients and one NT-treated patient ($p = 0.073$). Eight patients had atrial fibrillation (AF) on all Holter-recordings (two in HT and six in NT treated group), all with a history of chronic AF. In the NT group, one patient with preexisting chronic AF had a sustained sinus rhythm for 1 day after CA, whereas one HT-treated patient with AF after the resuscitation spontaneously recovered sinus rhythm after the rewarming period. No atrioventricular conduction blocks were detected.

In each group, one patient died of cardiogenic shock before 24 hours. In the HT group, the arrhythmias could be analyzed from all 36 0 to 24-hour recordings, but HRV analysis was gained for 30 subjects (missing HRV data: AF [n = 3], technical problems [n = 3]). The arrhythmias from 24- to 48-hour recording could be analyzed for 34 subjects (missing arrhythmia and HRV data: patient death [n = 1], technical problems [n = 1]), and HRV from 30 subjects (additional missing HRV data: AF [n = 3] technical problems [n = 1]). At 14 days, the arrhythmias could be analyzed from 28 subjects (missing arrhythmia and HRV data: patient death [n = 6], discharge to another hospital [n = 2]) and HRV from 26 subjects (additional missing HRV data: AF [n = 1], discharge to another hospital [n = 1]). In the NT group, the arrhythmias could be analyzed from all 34 0 to 24-hour recordings, but HRV analysis was done for 27 subjects (missing HRV data: AF [n = 6], pacemaker [n = 1]). The arrhythmias from 24- to 48-hour recordings could be analyzed for 31 subjects (missing arrhythmia and HRV data: patient death [n = 1], technical problems [n = 2]) and HRV for 25 subjects (addi-

Table 1. Clinical and demographic data of the patients

	Hypothermia (n = 36)	Normothermia (n = 34)
Age (yrs)	60 (23–75)	59 (18–75)
Male/female (%)	32/4 (89/11)	24/10 (71/29)
Bystander initiated cardiopulmonary resuscitation, n (%)	18 (50)	19 (56)
Basic life support (min)	7 (5–14)	7 (5–11)
Advanced cardiac life support (min)	14 (5–59)	13 (5–39)
ROSC (min)	18 (9–39)	18 (8–45)
Defibrillations before ROSC, n	3 (1–12)	2 (1–30)
Total dose of epinephrine before ROSC (mg)	2.0 (0–9.0)	2.0 (0–6.5)
Thrombolysis, n (%)	13 (36)	9 (26)
Glasgow Coma Scale score at admission	5 (3–7)	5 (3–8)
Tympanic temperature at admission (°C)	35.2 (33.4–36.9)	35.5 (33.6–36.9)
Inotropic agents used during the first 48 hrs, cumulative doses		
Dopamine (mg)	340 (0–2086)	382 (0–1934)
Dobutamine (mg)	0 (0–1856)	0 (0–692)
Norepinephrine (mg)	0.0 (0.0–17.1)	0.0 (0.0–12.4)
Epinephrine (mg)	0.0 (0.0–15.0)	0.0 (0.0–9.8)

ROSC, restoration of spontaneous circulation.

Data are given as median and range. None of the differences between the two groups are statistically significant.

tional missing HRV data: AF [n = 5] pacemaker [n = 1]). At 14 days, the arrhythmias could be analyzed for 22 subjects (missing arrhythmia and HRV data: patient death [n = 10], discharge to another hospital [n = 2]) and HRV for 16 subjects (additional missing HRV data: AF [n = 6]).

The results of the Holter analyses are presented in Table 2. The mean heart rate was significantly lower in the HT group than in the NT group during the first two recordings. Only two patients (both in the HT group) had an average heart rate <50 during the 0 to 24-hour recording (mean heart rates 37 and 49). The patient with the lowest mean heart rate received a temporary pacemaker that operated in ventricular inhibited mode only. The pacemaker did pace about 200 beats during the whole recording time only. None of the study patients had an average heart rate <50 during the 24 to 48-hour recording. The number of isolated PVBs and couplets was increased in the HT group during the first and second recording. The number of VTs or VFs did not differ between the treatment groups. The number of PVBs per hour during the 0–24 hour and 24–48 hour recordings did not differ between those with EF <35% and EF >35%, nor did the number of couplets. The median number of VTs during the 0–24-hour recording was two in the group with EF <35% and one in the group with EF >35% ($p = 0.027$), but the number of VTs during the 24–48-hour recording did not differ between EF <35% and EF >35% groups. At 14 days after CA, there were no significant differences in Holter variables between the groups. However, this recording represents mainly patients with good outcome, as most of the patients with poor outcome had already died before this time point.

VT requiring direct current cardioversion occurred in three patients: in two HT-group patients before the induction of HT (temperature >37°C in both cases) and in one NT-group patient. VF occurred in three patients randomized to the HT group and in one patient randomized to the NT group. In one HT-group patient with large anterior MI, VF occurred twice in a final phase of cardiogenic shock during actual HT. In another patient randomized to HT, VF occurred just after transfer to the ICU and before the induction of HT. The third HT-group patient had VF during the second recording, after the rewarming phase. The NT-group patient with VF during the first recording had an acute MI.

The HRV results are presented in Table 3. All the time-domain variables were significantly higher in the HT group during the first 24 hours. On the first recording, SDNN was <50 msec in none of the HT-group patients and in five of the NT-group patients ($p = 0.019$). On the second recording, the respective numbers were 1 and 7 ($p = 0.018$). SDNN and SDANN were significantly higher in HT

Table 2. Ambulatory ECG findings at 0–24 hrs, 24–48 hrs and 14 days after cardiac arrest

	Hypothermia	Normothermia	*p*
0–24-hr recording			
Mean heart rate (bpm)	68 (37–97)	82 (58–119)	<0.001
PVB/hr	35.7 (0.6–1047.8)	7.6 (0.1–173.2)	<0.001
Number of couplets	13 (0–778)	5 (0–209)	0.001
Number of VTs	1 (0–146)	1 (0–60)	0.685
Number of patients with at least one VT (%)	24 (67)	23 (74)	0.502
SVPB/hr	2.7 (0–125)	2.0 (0–397)	0.300
24–48-hr recording			
Mean heart rate (bpm)	85 (57–130)	91 (65–121)	0.160
PVB/hr	19.5 (0.1–797.5)	3.7 (0–146.8)	0.003
Number of couplets	5 (0–492)	1 (0–134)	0.021
Number of VTs	0.5 (0–104)	0 (0–27)	0.126
Number of patients with at least one VT (%)	17 (50)	10 (32)	0.147
SVPB/hr	2.2 (0–206)	1.4 (0–260)	0.545
14 days recording			
Mean heart rate (bpm)	70 (48–92)	75 (45–100)	0.197
PVB/hr	8.2 (0–1863.5)	3.5 (0–309.5)	0.148
Number of couplets	3 (0–605)	1 (0–127)	0.454
Number of VTs	0 (0–10)	0 (0–15)	0.612
Number of patients with at least one VT (%)	7 (25)	7 (32)	0.594
SVPB/hr	2.2 (0–206)	0.6 (0–101)	0.020

bpm, beats per minute; PVB, premature ventricular beat; VT, ventricular tachycardia; SVPB, supraventricular premature beat.

Data are given as median and range. In the hypothermia group, data are from 36 subjects (0–24-hr recordings), 34 subjects (24–48-hr recordings), or from 28 subjects (14-day recordings). In the normothermia group, data are from 34 subjects (0–24-hr recordings), from 31 subjects (24–48-hr recordings), or from 22 subjects (14-day recordings).

Table 3. Heart rate variability at 0–24 hrs, 24–48 hrs, and 14 days after cardiac arrest

	Hypothermia	Normothermia	*p*
SDNN (msec)			
0–24 hrs	136 (64)	71 (32)	<0.001
24–48 hrs	130 (61)	73 (30)	<0.001
14 days	83 (30)	79 (49)	0.358
SDANN (msec)			
0–24 hrs	127 (59)	70 (38)	<0.001
24–48 hrs	135 (64)	69 (30)	<0.001
14 days	68 (28)	68 (34)	0.766
Total power (msec)			
0–24 hrs	13.2 (6.8)	8.3 (5.3)	0.005
24–48 hrs	11.2 (5.7)	11.1 (7.6)	0.630
14 days	23.9 (15.9)	23.3 (24.6)	0.402
Low frequency (msec)			
0–24 hrs	9.9 (6.6)	5.7 (4.4)	0.002
24–48 hrs	7.6 (5.1)	7.2 (5.1)	0.653
14 days	14.4 (10.1)	12.0 (14.0)	0.083
High frequency (msec)			
0–24 hrs	8.2 (5.8)	4.8 (3.6)	0.004
24–48 hrs	5.8 (4.1)	5.2 (3.6)	0.639
14 days	8.9 (6.4)	8.8 (9.2)	0.438

SDNN, SD of individual normal-to-normal intervals; SDANN, SD of the averaged normal-to-normal intervals for all 5-min periods of the 24-hr recording.

Data are given as mean (SD). In the hypothermia group, data are from 30 subjects (0 to 24-hr and 24 to 48-hr recordings) or from 26 subjects (14 day recordings). In the normothermia group, data are from 27 subjects (0 to 24-hr recordings), from 25 subjects (24 to 48-hr recordings), or from 16 subjects (14-day recordings).

group also on the 24 to 48-hour recording. At 14 days after CA, none of these variables differed between the two groups. The frequency domain variables showed a similar pattern.

Outcome. At 6 months after CA, the outcome was favorable (CPC 1 or 2) in 69% (n = 25; CPC 1 in 22, CPC 2 in 3) of HT-treated patients and in 47% (n = 16; CPC 1 in 11, CPC 2 in 5) of NT-treated patients ($p = 0.057$). Outcome was poor in 11 HT-treated patients (CPC 3 in 2 and CPC 5 in 9) and in 18 NT-treated patients (CPC 3 in 4, CPC 4 in 1 and CPC 5 in 13). In the HT-group death occurred after a median of 13 days (range, 1–116 days) and in the NT group after a median of 9 days (range, 1–147 days).

Predictors of Outcome. In univariate analysis, the HRV variables associated with outcome in HT group were SDNN ($p = 0.013$), SDANN ($p = 0.018$), and LF ($p = 0.029$) of the 24 to 48-hour recording. In the NT group, none of these variables was associated with outcome. The following variables were chosen for the multivariate analysis: treatment group, ROSC delay (expressed in minutes), age (categorized as younger or older than 65 years), occurrence of VTs during the first 2 days (categorized as absent or present), EF on the second day TTE (categorized as < or >35%), and etiology of the CA (categorized as ischemic or nonischemic). The HRV variable chosen for the multivariate analysis was SDNN of the 24 to 48-hour recording [categorized as < or >100 msec (24)] based on univariate analysis results.

In multivariate analysis, the variables associated with good outcome were shorter ROSC delay ($p = 0.009$) with odds ratio 0.86 (95% confidence interval 0.77–0.96) and SDNN >100 msec of the 24 to 48-hour recording in the HT group ($p = 0.018$) with odds ratio 8.27 (95% confidence interval 1.47–46.48).

DISCUSSION

In this study, the use of therapeutic HT of 33°C for 24 hours after CA was safe, with no influence on clinically significant cardiac arrhythmogeneity. HT resulted in higher measures of HRV than for the NT group. A slight excess of ventricular premature beats occurred in patients treated with HT, but the number of VTs did not differ between the groups. The baseline levels of cardiac enzymes at admission to ICU were higher in patients randomized to HT treatment and, thereafter, throughout the early study period, indicating a larger infarct size in this group and an increased tendency to PVBs.

Only one VF episode occurred during the actual HT. The equal distribution of clinically significant ventricular tachyarrhythmias in the treatment groups is in concordance with previously published data (1, 2, 27, 28). In the entire Hypothermia After Cardiac Arrest study population, lethal or long-lasting arrhythmias were not significantly increased in HT-treated patients, and the study of Bernard et al reported no clinically significant cardiac arrhythmias in their HT-treated patients (1, 2). 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 (27). The study by Holzer et al (28) evaluating the safety of endovascular cooling after CA reported a statistically significant increase in transient bradycardia, but not tachyarrhythmias between admission and 32 hours after CA.

All HRV values were significantly higher in the HT group in the 0 to 24-hour recording than in normothermic controls, suggesting preserved autonomic modulation of the heart and a favorable effect of HT. The effect was carried throughout the 24 to 48-hour recording. At 14 days, no differences appeared between the treatment groups, but most of the patients with poor outcome had already died.

There are several possible explanations for the higher HRV values in the HT group. First, HRV is inversely associated with heart rate, and the increased HRV during HT may therefore be a physiologic phenomenon related to bradycardia (9). Patients assigned to HT treatment were cooled during the 0 to 24-hour recording and rewarmed during the 24 to 48-hour recording, which resulted first in decreasing and then increasing heart rate.

Second, there may also be a true temperature-induced change in autonomic nervous activity, which increases the HRV. MacKenzie et al (29) reported that four patients with severe thermolability (but no cardiovascular diseases) showed significantly enhanced HRV during steady HT (33.9°C ± 0.7°C), when compared with NT. The association of decreased temperature and increased HRV has also been shown in isolated rat hearts (30). The variability of interbeat intervals was always greater during HT than during the same heart rate induced pharmacologically. The authors concluded that low temperature may hamper the mutual synchronization of sinoatrial pacemaker cells in isolated rat heart (30).

Third, increased HRV might reflect a beneficial effect on myocardial function during HT. Cold cardioplegia and topical cooling have been used to protect the heart from ischemic injury during cardiopulmonary bypass surgery. Mild core HT in awake healthy human subjects is associated with increased myocardial perfusion (31). Although ischemic myocardial damage was already more pronounced in our HT patients, as demonstrated by the serum cardiac enzyme levels at admission, the echocardiograms recorded during the cooling period showed no difference in myocardial function.

Lastly, improved HRV may be related to neuroprotection by HT. We have previously reported that HT after CA was associated with decreasing levels of serum neuron specific enolase, which may indicate neuroprotection (32). 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 as sedative medication is decreased.

The use of therapeutic HT after CA may change or invalidate the prognostic value of serum biochemical markers (32), but the absence of early cortical responses in median nerve somatosensory-evoked potentials seem to accurately predict permanent coma also in these patients (33). Unfortunately, this method lacks sensitivity in identifying patients with poor outcome. Our results suggest that preserved HRV may be a predictor of favorable outcome after CA in patients treated with HT.

There are some limitations to this study. The ambulatory ECG recordings of patients assigned to HT reflect arrhythmias and HRV under changing temperature conditions, as these patients were first cooled during the 0–24-hour recording and then rewarmed during the 24–48-hour recording. Our results do not allow for correlating temperature levels with arrhythmias or HRV. However, the aim of this study was to examine the cardiac effects of the therapeutic HT protocol, as currently used in the treatment of patients with of out-of-hospital VF CA. There are no previous reports on the abil-

ity of early HRV measurements to predict outcome after CA. HRV assessed early after acute MI has, however, predicted short-term mortality and major complications (34). The sample size of the study and the follow-up period do not allow assessment of the effects on long-term outcome. Most patients received beta blockers during the first 48 hours, which could have raised the HRV and diminished its predictive value, although LF and SDNN have been reported to preserve their predictive ability during beta blockade (35, 36). Our patients also received inotropic drugs, but the two treatment groups did not differ in this aspect. Schmidt et al (16) have reported that in ICU patients with multiple organ dysfunction, the HRV time-domain and frequency domain indexes of the patients on catecholamines showed no significant differences from those not on catecholamines. Furthermore, long-range HRV indexes are partly dependent on the range of daily activity, and the level of activity can thus be a confounding factor at 14 days (37). All of our patients were immobilized during the first two Holter recordings, excluding the effect of physical activity. Because the majority of patients with poor outcome had already died before day 14, the results from day 14 recordings mainly represent patients with good outcome. Finally, in our study respiratory rate was not standardized during the recordings, which may be a confounding factor as respiratory variation influences HRV.

CONCLUSIONS

Therapeutic HT of 33°C in patients resuscitated from VF CA had a neutral effect on the occurrence of clinically significant cardiac arrhythmias. Despite higher baseline serum myocardial injury marker levels and increased number of PVBs, the patients treated with HT had a better outcome than patients assigned to NT. Although the improved HRV may not signify a cardioprotective effect, we found no evidence of an untoward effect on myocardial function with therapeutic HT.

Our results also suggest that HT may preserve autonomic regulation of the heart. It cannot be concluded whether the mechanism of action behind preserved HRV is the previously documented neuroprotective effect of HT, direct effect on heart rate, or both. Preserved HRV was associated with a more favorable outcome in HT-treated patients. The value of preserved HRV as a predictor of a favorable outcome in patients with CA treated with HT should be confirmed in a larger study.

REFERENCES

1. The Hypothermia After Cardiac Arrest study group: Mild therapeutic hypothermia to improve the neurologic outcome after CA. *N Engl J Med* 2002; 346:549–556
2. Bernard S, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; 346:557–563
3. van Alem AP, Post J, Koster RW: VF recurrence: Characteristics and patient outcome in out-of-hospital cardiac arrest. *Resuscitation* 2003; 59:181–188
4. White JD: Hypothermia: The Bellevue experience. *Ann Emerg Med* 1984; 11:417–424
5. Frank SM, Fleisher LA, Breslow MJ, et al: Perioperative maintenance of normothermia reduces the incidence of morbid cardiac events. A randomized clinical trial. *JAMA* 1997; 277:1127–1134
6. Hale SL, Kloner RA: Myocardial temperature in acute myocardial infarction: Protection with mild regional hypothermia. *Am J Physiol* 1997; 273:H220–H227
7. Simkhowich BZ, Hale SL, Kloner RA: Metabolic mechanism by which mild regional hypothermia preserves ischemic tissue. *J Cardiovasc Pharmacol Ther* 2004; 9:83–90
8. Task Force for the European Society of Cardiology and North American Society of Pacing and Electrophysiology: Heart rate variability. Standards of measurement, physiological interpretation and clinical use. *Circulation* 1996; 93:1043–1065
9. Kleiger RE, Miller JP, Bigger JT Jr, et al: Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59:256–262
10. Nolan J, Batin PD, Andrews R, et al: Prospective study of heart rate variability and mortality in chronic heart failure: Results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-Heart). *Circulation* 1998; 98:1510–1516
11. Huikuri HV, Linnaluoto MK, Seppänen T, et al: Circadian rhythm of heart rate variability in survivors of cardiac arrest. *Am J Cardiol* 1992; 70:610–615
12. Fei L, Anderson MH, Katritsis D, et al: Decreased heart rate variability in survivors of sudden cardiac death not associated with coronary heart disease. *Br Heart J* 1994; 71:16–21
13. Dougherty CM, Burr RL: Comparison of heart rate variability in survivors and nonsurvivors of sudden cardiac arrest. *Am J Cardiol* 1992; 70:441–448
14. Buchman TG, Stein PK, Goldstein B: Heart rate variability in critical illness and critical care. *Curr Opin Crit Care* 2002; 8:311–315
15. Gang Y, Malik M: Heart rate variability in critical care medicine. *Curr Opin Crit Care* 2002; 8:371–375
16. Schmidt H, Muller-Werdan U, Hoffmann T, et al: Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. *Crit Care Med* 2005; 33:1994–2002
17. Grogan EL, Morris JA, Norris PR, et al: Reduced heart rate volatility: An early predictor of death in trauma patients. *Ann Surg* 2004; 240:547–556
18. Lowensohn RI, Weiss M, Hon EH: Heart-rate variability in brain-damaged adults. *Lancet* 1977; 1:626–628
19. Leipzig TJ, Lowensohn RI: Heart rate variability in neurosurgical patients. *Neurosurgery* 1986; 19:356–362
20. Haji-Michael PG, Vincent JL, Degaute JP, et al: Power spectral analysis of cardiovascular variability in critically ill neurosurgical patients. *Crit Care Med* 2000; 28:2578–2583
21. Korpelainen JT, Sotaniemi KA, Huikuri HV, et al: Abnormal heart rate variability as a manifestation of autonomic dysfunction in hemispheric brain infarction. *Stroke* 1996; 27:2059–2063
22. Mäkikallio AM, Mäkikallio TH, Korpelainen JT, et al: Heart rate dynamics predict poststroke mortality. *Neurology* 2004; 62: 1822–1826
23. Cummins RO, Chamberlain DA, Abramson NS, et al: Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: The Utstein style: A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation* 1991; 84:960–975
24. Schiller NB, Shah PM, Crawford M, et al: Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; 2:358–367
25. The Joint European Society of Cardiology/American College of Cardiology Committee: Myocardial infarction redefined—A consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J* 2000; 21:1502–1513
26. Jennet B, Bond M: Assessment of outcome after severe brain damage. *Lancet* 1975; 1:480–484
27. Dixon SR, Whitbourn RJ, Dae MW, et al: Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol* 2002; 40:1928–1934
28. Holzer M, Mullner M, Sterz F, et al: Efficacy and safety of endovascular cooling after cardiac arrest: Cohort study and Bayesian approach. *Stroke* 2006; 37:1792–1797
29. MacKenzie MA, Aengevaeren WR, Hermus AR, et al: Electrocardiographic changes during steady mild hypothermia and normother-

mia in patients with poikilothermia. *Clin Sci (Lond)* 1992; 82:39–45
30. Langer SJ, Lambertz M, Langhorst P, et al: Interbeat interval variability in isolated working heart rats at various dynamic conditions and temperatures. *Res Exp Med* 1999; 199: 1–19
31. Frank SM, Satitpunwaycha P, Bruce SR, et al: Increased myocardial perfusion and sympathoadrenal activation during mild core hypothermia in awake humans. *Clin Sci (Lond)* 2003; 104:503–508
32. Tiainen M, Roine RO, Pettilä V, et al: Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. *Stroke* 2003; 34:2881–2886
33. Tiainen M, Kovala TT, Takkunen OS, et al: Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with therapeutic hypothermia. *Crit Care Med* 2005; 33:1736–1740
34. Carpeggiani C, L'Abbate A, Landi P, et al: Early assessment of heart rate variability is predictive of in-hospital death and major complications after acute myocardial infarction. *Int J Cardiol* 2004; 96:361–368
35. Niemelä MJ, Airaksinen KE, Huikuri HV: Effect of beta-blockade on heart rate variability in patients with coronary artery disease. *J Am Coll Cardiol* 1994; 23:1370–1377
36. Tapanainen JM, Thomsen PE, Kober L, et al: Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. *Am J Cardiol* 2002; 90:347–352
37. Roach D, Wilson W, Ritchie D, et al: Dissection of long-range heart rate variability: Controlled induction of prognostic measures by activity in the laboratory. *J Am Coll Cardiol* 2004; 43:2271–2277