Journal of the American College of Cardiology
Vol. 36, No. 3, 2000
© 2000 by the American College of Cardiology
ISSN 0735-1097/00/$20.00
Published by Elsevier Science Inc.
PII S0735-1097(00)00779-8

Cardiopulmonary Cerebral Resuscitation Using Emergency Cardiopulmonary Bypass, Coronary Reperfusion Therapy and Mild Hypothermia in Patients With Cardiac Arrest Outside the Hospital

Ken Nagao, MD,* Nariyuki Hayashi, MD,* Katsuo Kanmatsuse, MD, FACC,† Ken Arima, MD,† Jyoji Ohtsuki, MD,* Kimio Kikushima, MD,† Ikuyoshi Watanabe, MD†

Tokyo, Japan

OBJECTIVES The purpose of this study was to evaluate the efficacy of an alternative cardiopulmonary cerebral resuscitation (CPCR) using emergency cardiopulmonary bypass (CPB), coronary reperfusion therapy and mild hypothermia.

BACKGROUND Good recovery of patients with out-of-hospital cardiac arrest is still inadequate. An alternative therapeutic method for patients who do not respond to conventional CPCR is required.

METHODS A prospective preliminary study was performed in 50 patients with out-of-hospital cardiac arrest meeting the inclusion criteria. Patients were treated with standard CPCR and, if there was no response, by emergency CPB plus intra-aortic balloon pumping. Immediate coronary angiography for coronary reperfusion therapy was performed in patients with suspected acute coronary syndrome. Subsequently, in patients with systolic blood pressure above 90 mm Hg and Glasgow coma scale score of 3 to 5, mild hypothermia (34°C for at least two days) was induced by coil cooling. Neurologic outcome was assessed by cerebral performance categories at hospital discharge.

RESULTS Thirty-six of the 50 patients were treated with emergency CPB, and 30 of 39 patients who underwent angiography suffered acute coronary artery occlusion. Return of spontaneous circulation and successful coronary reperfusion were achieved in 92% and 87%, respectively. Mild hypothermia could be induced in 23 patients, and 12 (52%) of them showed good recovery. Factors related to a good recovery were cardiac index in hypothermia and the presence of serious complications with hypothermia or CPB.

CONCLUSIONS The alternative CPCR demonstrated an improvement in the incidence of good recovery. Based upon these findings, randomized studies of this hypothermia are needed. (J Am Coll Cardiol 2000;36:776–83) © 2000 by the American College of Cardiology

The ultimate goal of cardiopulmonary cerebral resuscitation (CPCR) is to improve long-term outcome in patients who have suffered cardiac arrest. To reach this goal, however, there are various difficult problems such as cardiac resuscitation, cerebral resuscitation, urgent and intensive treatment of primary disease and rehabilitation and long-term treatment of primary disease. The most difficult problem is cerebral resuscitation in patients who have had cardiac arrest outside the hospital. A campaign for enlightenment in the chain of survival (1) has been performed in each country, but satisfactory effects have not been obtained yet. It is estimated that each year 8,000 people in Tokyo and 65,000 people in Japan develop cardiac arrest outside the hospital, but the rate of good recovery is extremely low (1% to 2%) (2,3). Therefore, we prepared a new protocol of CPCR with emergency cardiopulmonary bypass (CPB), coronary reperfusion therapy and mild hypothermia, and, in order to evaluate the efficacy of CPCR, a prospective preliminary study was performed in patients with out-of-hospital cardiac arrest meeting the inclusion criteria.

From the *Department of Emergency and Critical Care Medicine and the †Department of Cardiology, Nihon University School of Medicine, Tokyo, Japan.
Manuscript received June 25, 1999; revised manuscript received March 13, 2000, accepted April 14, 2000.

METHODS

Tokyo emergency medical system (2). Tokyo has an area of 1,750 km^2, and its daytime and nighttime population in 1997 was estimated at 14,410,000 and 11,430,000, respectively. The public emergency medical service activity system of Tokyo consists of an ambulance unit, an aviation unit and a telephone information unit. The ambulance unit is organized with three emergency medical service personnel, at least one of whom is a licensed emergency life-saving technician (ELST) who passed the national examination after the emergency life-saving development course (≥835 h). The ELST has been authorized by the minister of health and welfare to treat for cardiac arrest through maintenance of the airway with a laryngeal mask or double balloon tube, intravenous infusion of drugs, and defibrillation with a semi-automatic defibrillator. The rules of the ambulance unit for cardiac arrest outside the hospital provide that the ELST cannot make a decision to stop

Abbreviations and Acronyms

ACLS = advanced cardiac life support
CPB = cardiopulmonary bypass
CPCR = cardiopulmonary cerebral resuscitation
CPR = cardiopulmonary resuscitation
ELST = emergency life-saving technician
IABP = intra-aortic balloon pumping
PTCA = percutaneous transluminal coronary angioplasty
ROSC = return of spontaneous circulation
TIMI = thrombolysis in myocardial infarction
VF = ventricular fibrillation

cardiopulmonary resuscitation (CPR) and has to transport all patients, except for obviously dead bodies (such as a decapitation or postmortem rigidity), to the nearest emergency hospital. Consequently, each year about 96% of the patients with out-of-hospital cardiac arrest are transported under CPR by emergency medical service personnel.

Selection of patients. Patients who met all of the following new inclusion criteria of CPCR were enrolled in this study.

1. Patients age 18 to 74.
2. Patients who were witnessed having an arrest after chest pain, who cried out for help or were heard falling and were found immediately after arrest and whose first CPR was initiated within 15 min after arrest, or whose electrocardiogram recorded by the ELST demonstrated ventricular fibrillation (VF).
3. Patients who were ruled not to have acute aortic dissection and intracranial hemorrhage during resuscitation.
4. Patients with Glasgow coma scale score (4) between 3 and 5 upon arrival at an emergency room.

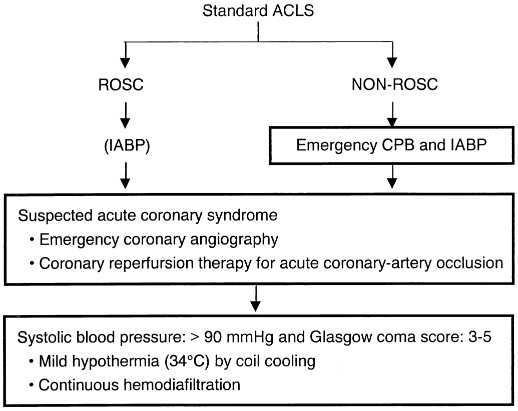

Figure 1. Treatment protocol. Standard ACLS was initiated in patients with cardiac arrest on arrival at the emergency room. When ROSC could not be achieved, emergency CPB plus IABP were immediately performed. In the cases of suspected acute coronary syndrome, emergency coronary angiography or coronary reperfusion therapy for acute coronary-artery occlusion were subsequently performed. When patient's systolic blood pressure was increased above 90 mm Hg and Glasgow coma scale score was between 3 and 5, mild hypothermia by coil cooling was induced. ACLS = advanced cardiac life support; CPB = cardiopulmonary bypass; IABP = intraaortic balloon pumping; ROSC = return of spontaneous circulation.

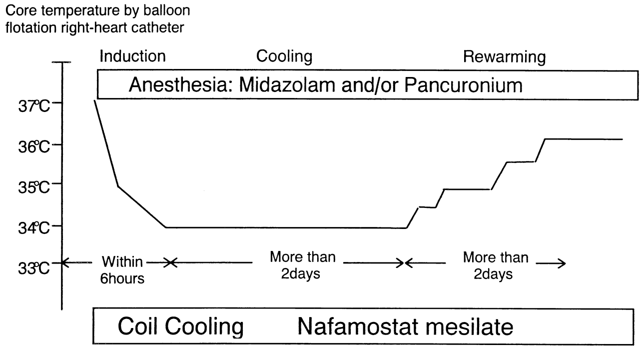

Figure 2. Mild hypothermia for cerebral resuscitation in patients with out-of-hospital cardiac cause of arrest. As a cooling method, coil cooling, which cools the blood circuit of continuous hemodiafiltration directly was used. As core temperature, pulmonary arterial blood temperature was monitored continuously by using a balloon flotation right-heart catheter. Induction and rewarming were conducted by two step down and slow step up methods, respectively. Hypothermia (34°C) at cooling stage continued for at least two days. Midazolam and pancuronium were used for anesthesia during this period, and nafamostat mesilate was used for control of coagulant.

5. Patients whose families gave informed consent to the new CPCR therapy.

Treatment protocol. Treatment protocol in this study is shown in Figure 1. The patient with out-of-hospital cardiac arrest was assessed for the cardiac cause of arrest meeting the inclusion criteria as soon as possible, and the new CPCR, according to the treatment protocol, was initiated.

Cardiac resuscitation—advanced cardiac life support (ACLS) according to the guideline of the Emergency Cardiac Care and American Heart Association (1) was initiated in patients with cardiac arrest upon arrival at the emergency room. When return of spontaneous circulation (ROSC) could not be achieved in patients with VF after unsynchronized electric shocks, with the second administration of epinephrine, or in patients without VF after the second administration of epinephrine, emergency CPB and intra-aortic balloon pumping (IABP) were immediately performed in the emergency room. On the other hand, IABP was immediately performed in patients who achieved ROSC with standard ACLS before or after arrival at the emergency room and who did not show improved hemodynamic collapse. Then, assessment of ischemic cardiac arrest was made, and in the case of suspected acute coronary syndrome, emergency coronary angiography was subsequently performed. When acute coronary syndrome-related artery was obstructed with thrombolysis in myocardial infarction (TIMI) (5) flow grade 0 or 1, or was delayed with TIMI flow grade 2, percutaneous transluminal coronary angioplasty (PTCA) was performed.

Cerebral resuscitation—when a patient's systolic blood pressure was increased above 90 mm Hg by ACLS and Glasgow coma scale score (4) was between 3 and 5, mild hypothermia was induced. Procedure of mild hypothermia (34°C) was performed by the direct blood cooling method with a coil (6). Pulmonary arterial blood temperature was monitored continuously as core temperature by using bal-

JACC Vol. 36, No. 3, 2000
September 2000:776–83

loon flotation right-heart catheter. Mild hypothermia was maintained for at least two days (fundamentally for three days) and was induced by two-stage cooling (7) to reach 34°C within 6 h after initiation of cooling. Rewarming (7) was conducted slowly and gradually and took at least two days (warming by 0.5°C every 12 h then maintained at 35°C for 24 h) (Fig. 2). Patient's condition during mild hypothermia was controlled as follows: systolic blood pressure 90 mm Hg or more, cardiac index 2.2 $l/min/m^2$ or more, systemic oxygen delivery 520 $ml/min/m^2$ or more, hemoglobin 12 g/dl or more, oxygen extraction ratio between 20% and 30% and activated coagulation time between 150 and 200 s by using the anticoagulant nafamostat mesilate. Anesthetics used during mild hypothermia were the gamma-aminobutyric acid-agonist midasolam and the muscle relaxant pancuronium (7). Furthermore, patients were nourished by complete parenteral nutrition during mild hypothermia. Water and electrolyte balances were controlled by continuous hemodiafiltration, and blood circulating in this hemodiafiltration cycle was cooled and used for hypothermia by coil cooling (6).

Data collection and neurologic outcome. Clinical data were obtained from a standardized form in our department according to the recommendations of the Utstein consensus conference (8). Baseline characteristics such as age, gender, location of arrest, initial cardiac rhythm, principal event-to-event intervals, Glasgow coma scale score, initial arterial blood gas and other clinically important characteristics were recorded. Acute coronary artery occlusion of patients with suspected acute coronary syndrome was assessed by at least three interventional cardiologists. The neurologic outcome at hospital discharge was assessed according to the cerebral performance categories (9) as follows: 1) good cerebral performance, 2) moderate cerebral disability, 3) severe cerebral disability, 4) coma or vegetative state, and 5) brain death or death.

Statistical analysis. Values were expressed as mean ± SD. Factors potentially relevant to good cerebral performance were assessed by univariate analysis with the chi-square test for categorical variables. A two-tailed p value of <0.05 was considered to indicate statistical significance. Predictors found to be significant on the basis of univariate analysis were then included in a forward, stepwise multiple logistic-regression model to identify the independent factors associated with a good recovery. Statistical analysis was performed with the Stata 4.0 statistical package for Macintosh (Stata, College Station, Texas).

RESULTS

Characteristics of the patients. From January 1996 to April 1998, 287 of the 18,247 patients with out-of-hospital cardiac arrest in Tokyo were transported to our emergency room. A total of 50 patients were treated after meeting the inclusion criteria with CPCR in this study. Characteristics of the 50 patients are shown in Table 1 in the column marked "all patients." The rate of bystander-initiated CPR was 40%, and the time interval from cardiac arrest to initiation of CPR was 7.9 ± 6.9 min. With regard to initial cardiac rhythm at the scene, 84% showed VF, and the remaining patients also showed VF subsequently. The rate of ROSC was 92% (14% of patients achieved ROSC before arrival at the hospital by emergency medical service personnel, and 78% achieved ROSC after arrival at the emergency room). The time interval from cardiac arrest to ROSC was 66.6 ± 42.5 min. The procedure of ACLS was standard ACLS in 28% and emergency CPB plus IABP in 72%. The cardiac cause of arrest was acute coronary syndrome in 78%, hypertrophic cardiomyopathy in 12% and myocarditis in 4%.

Cardiac catheterization and coronary intervention. Table 2 shows angiographic data of all 39 patients with suspected acute coronary syndrome and those after PTCA for TIMI flow grades 0 to 2. The initial angiogram of acute coronary syndrome related artery revealed TIMI flow grades 0 to 2 in 77% (30/39) of the patients. Eighty-seven percent (26/30) of these arteries with TIMI flow grades 0 to 2 successfully restored anterograde flow of TIMI flow grade 3 by PTCA. In cases of non-ROSC, coronary flow was assessed by TIMI flow grade under CPB and IABP. Three of four patients who had a lesion with TIMI flow grade 3 and insignificant stenosis survived and were observed having coronary spasm by the acethylcholine load test (10) in chronic stage.

Data of mild hypothermia. Of 50 patients who underwent CPCR in this study, 46 patients continued ROSC (carotid arterial pulses were palpable and invasive arterial pressure was detectable) for more than 1 h. Mild hypothermia could be induced in 23 of these ROSC patients as systolic blood pressure increased to 90 mm Hg or more. Characteristics of the 23 patients are shown in Table 1 as patients undergoing hypothermia, and coronary angiographic data are shown in Table 2 as patients undergoing hypothermia. Table 3 shows data of mild hypothermia treatment. The mean core temperature was 34.2 ± 0.8°C during the cooling stage. The mean induction time from initiation of cooling to reaching 34°C was 6.3 ± 3.4 h, the mean duration of cooling stage was 71.0 ± 49.1 h, and the mean rewarming time to 36°C was 43.9 ± 5.3 h.

Neurologic outcome. Table 4 shows cerebral performance categories at hospital discharge of 23 patients with mild hypothermia. The good cerebral performance rates of patients whose Glasgow coma score before hypothermia was 3, 4 or 5 were 35.7% (5/14), 100% (5/5) and 50% (2/4), respectively. The good cerebral performance rate of the entire 23 patients was 52.2% (12/23), and the survival discharge rate was 65.2% (15/23).

Cause of death. Of 36 patients who underwent emergency CPB plus IABP, four died without achieving ROSC, and 23 died without getting satisfactory improvement of hemodynamic collapse. Of 23 patients with mild hypothermia, two died of severe sepsis (11) as one of serious complications

Table 1. Baseline Characteristics of All 50 Patients and 23 Patients Undergoing Hypothermia*

Characteristics	All Patients (n = 50)	Patients Undergoing Hypothermia (n = 23)
Age—yr	54.5 ± 14.3	52.3 ± 16.6
Male gender—n (%)	35 (70)	15 (65.2)
History of coronary artery disease or surgery—n (%)†	5 (10)	2 (8.7)
Bystander initiating CPR—n (%)	20 (40)	10 (43.5)
Chest pain before cardiac arrest—n (%)	16 (32)	6 (26.1)
Location of cardiac arrest—n (%)		
At home	4 (8)	3 (13.0)
At public place		
At work	16 (32)	6 (26.1)
Other	30 (60)	14 (60.9)
Initial cardiac rhythm—n (%)		
Ventricular fibrillation	42 (84)	21 (91.3)
Asystole	5 (10)	1 (4.3)
Pulseless electrical activity	3 (6)	1 (4.3)
Time from cardiac arrest to initiation of CPR—min	7.9 ± 6.9	7.5 ± 7.0
Time from cardiac arrest to emergency room—min	23.4 ± 14.9	24.4 ± 12.5
Time from emergency room to initiation of CPB—min (n)	37.6 ± 25.1 (36)	34.9 ± 21.1 (9)
Location of ROSC—n (%)		
Before hospital	7 (14)	7 (30.4)
At emergency room	39 (78)	16 (69.6)
Time from cardiac arrest to ROSC—min (n)	66.6 ± 42.5 (46)	58.1 ± 37.0 (23)
Glasgow coma score		
Arrival at emergency room	3.4 ± 0.7	3.4 ± 0.7
Before hypothermia		3.6 ± 0.8
Initial arterial blood gas		
pH	7.16 ± 0.21	7.25 ± 0.15
Base excess—mmol/L	−13.0 ± 8.2	−9.9 ± 7.2
Systolic blood pressure—mm Hg		
Before hypothermia		120.1 ± 22.4
Suspected cardiac cause of arrest—n (%)		
Acute coronary syndrome	39 (78)	16 (69.6)
Hypertrophic cardiomyopathy	6 (12)	4 (17.4)
Myocarditis	2 (4)	1 (4.3)
Idiopathic ventricular fibrillation	1 (2)	1 (4.3)
Unknown	2 (4)	1 (4.3)
Procedure of ACLS—n (%)		
Standard ACLS	14 (28)	14 (60.9)
CPB and IABP after failed standard ACLS	36 (72)	9 (39.1)

*Values are expressed as mean ± SD; †Coronary artery disease or surgery was defined as angina, prior myocardial infarction, percutaneous transluminal coronary angioplasty or coronary-artery bypass grafting.

ACLS = advanced cardiac life support; CPB = cardiopulmonary bypass; CPR = cardiopulmonary resuscitation; IABP = intraaortic balloon pumping; ROSC = return of spontaneous circulation.

of hypothermia, five died of exacerbation of hemodynamic collapse during cooling, and two died of bleeding due to vessel injury at the insert site of CPB catheter.

Predictive factors of good recovery. Figure 3 shows the results of analysis of factors relevant to good cerebral performance in 23 patients with mild hypothermia. Cardiac index in cooling stage (odds ratio, 17.5; 95% confidence interval, 2.4 to 129.7; $p < 0.01$) and systemic oxygen delivery (odds ratio, 10; 95% confidence interval, 1.2 to 83.2; $p = 0.03$) were shown to be the factors associated with good cerebral performance. Furthermore, stepwise regression analysis including factors of cooling stage (core temperature, duration, hemoglobin, cardiac index, arterial oxygen content and oxygen extraction ratio) and the presence of serious complications with severe sepsis (11) or a large quantity of bleeding (blood transfusion of more than 2,000 ml was required) revealed that the cardiac index and serious complications were related to good cerebral performance—good cerebral performance = 0.13−0.56 (presence of serious complications with CPB or mild hypothermia) +0.18 (cardiac index in mild hypothermia at cooling stage), $r = 0.683$, $p = 0.0091$ (good cerebral performance indicates one and the other categories of cerebral performance indicate zero).

DISCUSSION

Conventional ALCS. There are reports on some multicenter randomized standard ACLS clinical trials in patients with out-of-hospital cardiac arrest (12–15). The European

Table 2. Angiographic Data in All 39 Patients and in 16 Patients Undergoing Hypothermia Who Underwent Angiography for Suspected Acute Coronary Syndrome

Variable	All Patients (n = 39)	Patients With Hypothermia (n = 16)
Initial coronary angiography of acute coronary syndrome-related artery		
TIMI flow grade 0 or 1—n (%)	26 (66.7)	12 (75)
Left main artery	1	0
Left anterior descending artery	17	7
Left circumflex artery	2	1
Right coronary artery	6	4
TIMI flow grade 2 and significant stenosis—n (%)	4 (10.3)	0 (0)
Left main artery	0	0
Left anterior descending artery	1	0
Left circumflex artery	2	0
Right coronary artery	1	0
TIMI flow grade 3 and significant stenosis—n (%)	5 (12.8)	1 (6.3)
Left main artery	3	1
Three-vessel disease	2	0
TIMI flow grade 3 and insignificant stenosis—n (%)	4 (10.3)	3 (18.7)
After coronary intervention for TIMI flow grades 0–2—n		
TIMI flow grade 0 or 1	2	1
TIMI flow grade 2	2	1
TIMI flow grade 3	26	10

TIMI = thrombolysis in myocardial infarction.

epinephrine study (15) was conducted in 3,327 patients with out-of-hospital cardiac arrest and compared the efficacy of standard-dose epinephrine with that of high-dose epinephrine. There were no significant differences in the survival discharge rate between the two groups, and subgroup analysis revealed that the survival rate of patients with witnessed arrest with suspected cardiac cause was 3.0% (58/1,939) and that of patients with initial rhythm of VF was 7.4% (42/564). Furthermore, the survival discharge rate of patients who underwent active compression-decompression ACLS in the standard-dose epinephrine group was 3.6% (18/496). On the other hand, there was no multicenter randomized ACLS clinical trial in Japan. Katsurado et al. (3) reported that the one-month survival rate with conventional ACLS in Japan was 2.6% in all 31,206 patients with out-of-hospital cardiac arrest and 8.9% in patients with cardiac arrest who were observed and resuscitated initially by bystanders. In our previous study (16), the good recovery rate with conventional ACLS was 1.1% in all 808 patients with out-of-hospital cardiac arrest and 3.2% in VF patients upon arrival at the hospital. Therefore, it is conceivable that this may be a limit of resuscitation by conventional ACLS.

Table 3. Data of Mild Hypothermia Treatment*

Time from emergency room to initiation of the hypothermia—h	2.1 ± 1.9
Time from initiation of the hypothermia to 34°C—h	6.3 ± 3.4
Cooling stage	
Core temperature—°C	34.2 ± 0.8
Duration—h	71.0 ± 49.1
Cardiac index—l/min/m^2	2.7 ± 1.4
Systemic oxygen delivery—ml/min/m^2	505 ± 296
Oxygen extraction ratio—%	30 ± 6
Hemoglobin—g/dl	12.9 ± 2.9
Platelet count—10^3/mm^3	262 ± 150
Activated coagulation time—s	191 ± 22
Duration of rewarming—h	43.9 ± 5.3

*Values are expressed as mean ± SD.

Emergency CPB and coronary reperfusion therapy. Currently, emergency CPB is performed in patients with cardiac arrest who do not respond to standard ACLS, patients with cardiogenic shock who are unresponsive to pressors and patients with pulmonary embolism (17–19). However, the efficacy of emergency CPB in cardiac arrest outside the hospital has been poor, and good recovery has rarely been obtained so far. The authors performed emergency CPB and immediate coronary reperfusion therapy in patients with acute myocardial infarction complicated with conventional ACLS-resistive VF. Return of spontaneous circulation was achieved in 88.5% of those patients, but the good recovery rate was low at 3.8% (20). Therefore, we considered that emergency CPB and immediate coronary reperfusion therapy may control a progression of myocardial ischemia and be a useful strategy for cardiac resuscitation, but further measures aimed at cerebral resuscitation are required. Spaulding et al. (21) reported that the survival discharge rate was 38.1% (32/84) in survivors with out-of-hospital cardiac arrest who received immediate angiography and PTCA, and successful PTCA was the independent factor of survival. However, Spaulding et al. (21) evaluated the efficacy in patients who had reached stable hemody-

Table 4. Cerebral Performance Categories at Hospital Discharge in 23 Patients Undergoing Mild Hypothermia

	Cerebral Performance Categories				
Glasgow Coma Score Before Hypothermia	**Good Cerebral Performance**	**Moderate Cerebral Disability**	**Severe Cerebral Disability**	**Coma or Vegetative State**	**Brain Death or Death**
3 (n = 14)	35.7% (n = 5)	7.1% (n = 1)		14.3% (n = 2)	42.9 (n = 6)
4 (n = 5)	100% (n = 5)				
5 (n = 4)	50% (n = 2)				50% (n = 2)

namic state upon arrival at the emergency room, and they did not describe cerebral resuscitation.

Hypothermia therapy. In recent years, hypothermia treatment using the surface cooling method has been performed with the aim of brain protection in patients with severe traumatic brain injury (22–25). There have been many reports on the mechanism of brain protection by hypothermia treatment, such as decrease in cerebral metabolism (26), preservation of high-energy phosphate stores (26), prevention of intracellular Ca^{2+} accumulation (27,28), prevention of cerebral thermo-pooling (29), preservation of blood-brain barrier (30), reduction of extracellular concentrations of excitatory neurotransmitters (25,31,32) and suppression of inflammatory response (25,33,34), but the complete mech-

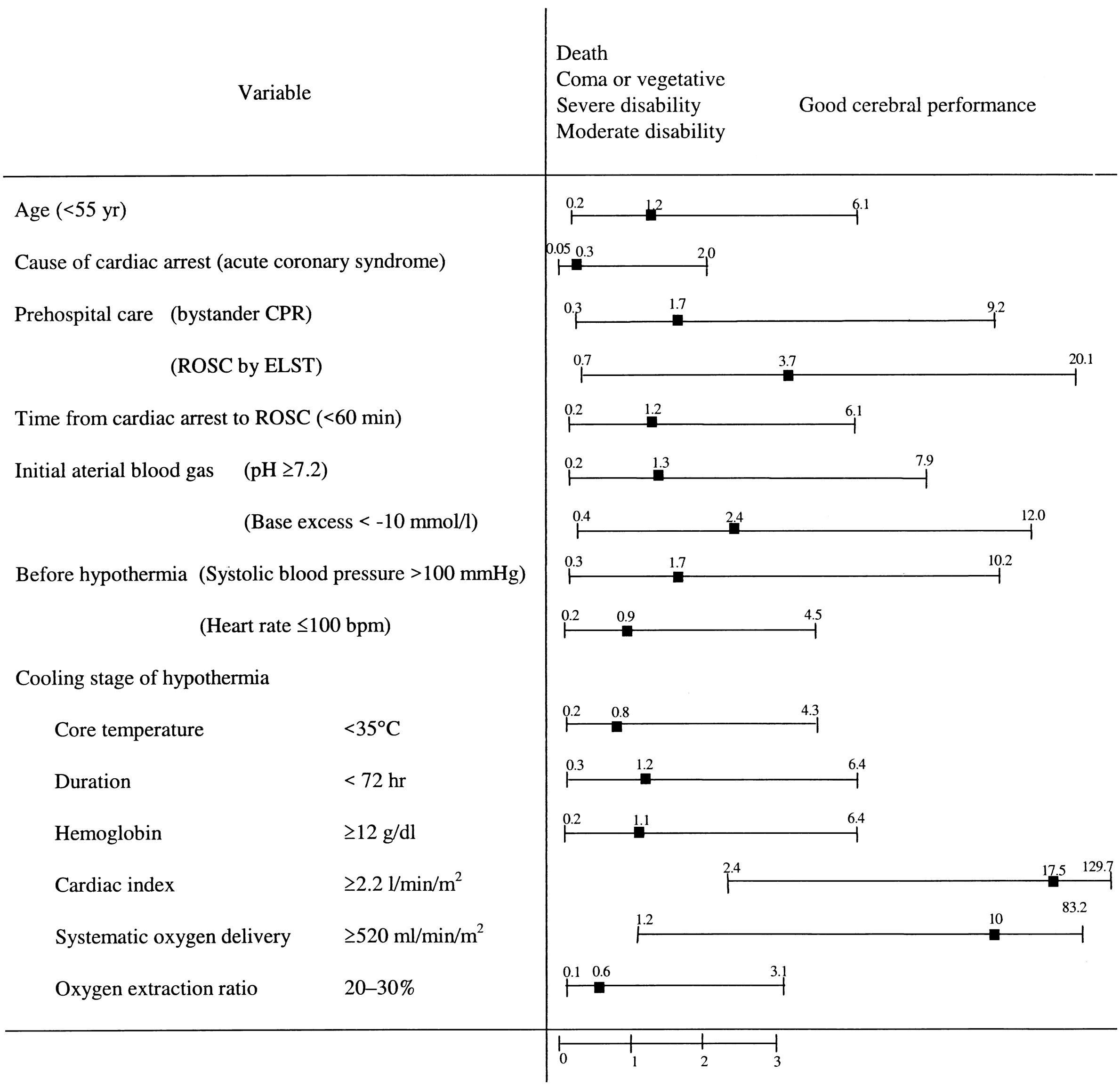

Figure 3. Factors relevant to good recovery in 23 patients with mild hypothermia. Point estimates and 95% confidence intervals for the odds ratios for good recovery at hospital discharge in several prospectively defined subgroups, according to cerebral performance categories. CPR = cardiopulmonary resuscitation; ELST = emergency life-saving technician; ROSC = return of spontaneous circulation.

anism remains to be elucidated. Moreover, the hypothermia treatment on procedure of cooling, degree of core temperature, duration in cooling stage and technique of induction and rewarming has not been established. By applying hypothermia treatment, we performed CPCR. Hypothermia was controlled according to the Hayashi method (7,29,35) except for monitoring of intracranial pressure, and the cooling procedure we used was the coil cooling method by direct blood cooling (6) because the coil cooling method was not laborious and a more precise control of core temperature could be exerted than with the surface cooling method. As for the overall results, the survival discharge rate and the good recovery rate were 30% (15/50) and 24% (12/50), respectively. These results were superior by two to five times those of conventional ACLS in patients with out-of-hospital VF reported so far (15,16,36). With regard to the 23 patients undergoing mild hypothermia, these rates were 65.2% (15/23) and 52.2% (12/23), respectively. Bernard et al. (37) reported that the good recovery rate at hospital discharge was 36.4% (8/22) in survivors who arrived comatose at the emergency room after out-of-hospital cardiac arrest and who were treated with moderate hypothermia (33°C for 12 h) by the surface cooling method. In comparison with Bernard's study, the good recovery rate in our patients with mild hypothermia was better. Furthermore, 70% of our study patients with mild hypothermia did not achieve ROSC upon arrival at the emergency room. It was considered that the present patients presented with more severe conditions for resuscitation than Bernard's patients. The analysis of factors related to good cerebral performance during mild hypothermia treatment revealed that the cardiac index in cooling stage and the presence of serious complications (severe sepsis under hypothermia and bleeding at the insert site of the CPB catheter) were the predicting factors. Infections (particularly pulmonary infection), coagulation disorders and cardiac arrhythmia have been reported as complications of hypothermia, and it has been considered that these complications may be caused by core temperature below 30°C or a cooling period longer than 24 h (38,39). In this study, we performed hypothermia treatment induced by the coil cooling method at 34°C for at least two days, which did not cause clinically significant arrhythmia or bleeding (except for bleeding due to vessel injury at the insert site of the CPB catheter), but two patients died of severe sepsis that caused pulmonary infection. Therefore, it is suggested that further infection-control measures and a specific technique to secure a vessel for CPB catheter insert with only one puncture are required.

Study limitations. There is a limitation in this study because this was not a randomized controlled study and the case number was small. Moreover, there is the problem that this treatment is more expensive than conventional CPCR. Linder et al. (40) reported that a significantly larger proportion of patients treated with vasopressin than of those treated with epinephrine were resuscitated successfully from out-of-hospital VF and survived for 24 h, but the neurological outcomes were similar. Therefore, cardiac resuscitation by ACLS with vasopressin and with coronary reperfusion therapy for acute coronary-artery occlusion and subsequent cerebral resuscitation by hypothermia should be evaluated hereafter. In conclusion, treatment with mild hypothermia by coil cooling, as indicated in patients with out-of-hospital cardiac cause of arrest who achieved ROSC by standard ACLS or emergency CPB plus IABP and who received coronary reperfusion therapy in acute coronary syndrome, may have improved chances of good recovery. Based on these findings, randomized studies of mild hypothermia for cerebral resuscitation in comatose survivors of out-of-hospital cardiac arrest are needed.

Reprint requests and correspondence: Dr. Ken Nagao, Surugadai Nihon University Hospital 1-8-13, Kanda Surugadai, Chiyoda-ku, Tokyo 101-8309, Japan.

REFERENCES

1. Emergency Cardiac Care Committee and Subcommittees, American Heart Association (ECC and AHA). Guidelines for cardiopulmonary resuscitation and emergency cardiac care. JAMA 1992;268:2171–95.
2. Tokyo Fire Department. Prehospital care [In Japanese]. In: Emergency Medical Service Division of Tokyo Fire Department, editor. The Actual Situation of Emergency Medical Services in Tokyo. Tokyo: Sankei, 1998;33–43.
3. Katsurada K, Kamijima G. Outcome of prehospital cardiopulmonary resuscitation by ambulance personnel in Japan—recent improvement in the outcome by "ELST" system [In Japanese]. J Jpn Assoc Acute Med 1997;8:131–7.
4. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. Lancet 1974;2:81–4.
5. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. Circulation 1987; 76:142–54.
6. Nagao K, Miki T, Okamoto K, et al. Blood cooling system using coil cooling for brain hypothermia [In Japanese]. Jpn J Acute Med 1999;23:674–704.
7. Hayashi N. Combination therapy of cerebral hypothermia, pharmacological activation of the dopamine system and hormonal replacement in severely brain damaged patients [In Japanese]. J Jpn Soc Intensive Care Med 1997;4:191–7.
8. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein style. Ann Emerg Med 1991;20:861–74.
9. Safar P. Cerebral resuscitation after cardiac arrest: a review. Circulation 1986;74:Suppl IV:IV138–53.
10. Yasue H, Horio Y, Nakamura N, et al. Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. Circulation 1986;74:955–63.
11. Members of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee: American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864–74.
12. Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. N Engl J Med 1992;327:1051–5.
13. Choux C, Gueugniaud PY, Barbieux A, et al. Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital. Resuscitation 1995;29:3–9.
14. Callaham M, Madsen DC, Barton CW, Sauders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine

versus standard-dose epinephrine in prehospital cardiac arrest. JAMA 1992;268:2667–72.
15. Gueugniaud PY, Mols P, Goldstein P, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. N Engl J Med 1998;339:1595–601.
16. Nagao K, Ohba T, Arima K, et al. Effects of sodium bicarbonate and epinephrine hydro-chloride in cardiac resuscitation [In Japanese]. J Jpn Assoc Acute Med 1992;4:99–107.
17. Hartz R, LoCicero J, Sanders JH, Jr, et al. Clinical experience with portable cardiopulmonary bypass in cardiac arrest patients. Ann Thorac Surg 1990;50:437–41.
18. Rees MR, Browne T, Sivananthan UM, et al. Cardiac resuscitation with percutaneous cardiopulmonary support. Lancet 1992;340:513–4.
19. Overlie PA, Walter PD, Hurd Hp II, et al. Emergency cardiopulmonary support with circulatory support devices. Cardiology 1994;84: 231–7.
20. Nagao K, Satou K, Arima K, Watanabe I, Yamashita M, Kanmatsuse K. Pathological conditions and strategies of patients with ventricular fibrillation complicating acute myocardial infarction [In Japanese]. In: Furuse A, editor. Frontiers in Cardiology. Tokyo: International, 1997:63–73.
21. Spaulding CM, Joly LM, Rosenberg A, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 1997;336:1629–33.
22. Shinozaki T, Sugimoto H, Taneda M, et al. Effect of mild hypothermia on uncontrollable intracranial hypertension after severe head injury. J Neurosurg 1993;79:363–8.
23. Clifton GL, Allen S, Barrodale P, et al. A phase II study of moderate hypothermia in severe brain injury. J Neurotrauma 1993;10:263–71.
24. Marion DW, Obrist WD, Carlier PM, Penrod LE, Darby JM. The use of moderate therapeutic hypothermia for patients with severe head injuries: a preliminary report. J Neurosurg 1993;79:354–62.
25. Marion DW, Fenrod LE, Kelsey SF, et al. Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 1997;336: 540–6.
26. Bering EA, Jr. Effect of body temperature change on cerebral oxygen consumption of the intact monkey. Am J Physiol 1961;200:417–9.
27. Mitani A, Kadoya F, Kataoka K. Temperature dependence of hypoxia-induced calcium accumulation in gerbil hippocampal slices. Brain Res 1991;562:159–63.
28. Churn SB, Taft WC, Billingsley MS, et al. Temperature modulation of ischemic neuronal death and inhibition of calcium/calmodulin-dependent protein kinase II in gerbils. Stroke 1990;21:1715–21.
29. Hayashi N, Hirayama T, Utagawa A. The cerebral thermo-pooling and hypothermia treatment of critical head injury patients. In: Nagai H, Kamiya K, editors. Intracranial Pressure IX. Tokyo: Springer-Verlag, 1994:589–99.
30. Smith SL, Hall ED. Mild pre- and posttraumatic hypothermia attenuates blood-brain barrier damage following controlled cortical impact injury in the rat. J Neurotrauma 1996;13:1–9.
31. Busto R, Globus MYT, Dietrich WD, et al. Effect of mild hypothermia on ischemia-induced release of neurotransmitters and free fatty acids in the rat brain. Stroke 1989;20:904–10.
32. Mitani A, Kataoka K. Critical levels of extracellular glutamate mediating gerbil hippocampal delayed neuronal death during hypothermia: brain microdialysis study. Neuroscience 1991;42:661–70.
33. Kader A, Frazzini VI, Baker CJ, et al. Effect of mild hypothermia on nitric oxide synthesis during focal cerebral ischemia. Neurosurgery 1994;35:272–7.
34. Kil HY, Zhang J, Piantadosi CA. Brain temperature alters hydroxyl radical production during cerebral ischemia/reperfusion in rats. J Cereb Blood Flow Metab 1996;16:100–6.
35. Hayashi N. The adverse treatment, brain hypothermia and replacement therapy for severe brain injury. International satellite meeting of brain hypothermia (abstr). 1998;31–4.
36. Herlitz J, Ekström L, Wennerblom B, Axelsson Å, Bång A, Holmberg S. Adrenaline in out-of-hospital ventricular fibrillation. Does it make any difference? Resuscitation 1995;29:195–201.
37. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. Ann Emerg Med 1997;30:146–53.
38. Mouritzen CV, Andersen MN. Mechanisms of ventricular fibrillation during hypothermia: relative changes in myocardial refractory period and conduction velocity. J Thorac Cardiovasc Surg 1966;51:579–84.
39. Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. Crit Care Med 1992;20:1402–5.
40. Lindner KH, Dirks B, Strohmenger HU, Prengel AW, Lindner IM, Lurie KG. Randomized comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. Lancet 1997;349: 535–7.