21. Shinn SH, Lee YT, Sung K, et al. Efficacy of emergent percutaneous cardiopulmonary support in cardiac or respiratory failure: fight or flight? Interact Cardiovasc Thorac Surg 2009;9:269-73.

We retrospectively evaluated early outcome and conducted this study to determine the predictive factors for percutaneous cardiopulmonary support (PCPS) weaning and hospital discharge. From January 2004 to December 2006, 92 patients diagnosed as cardiac or respiratory failure underwent PCPS using the Capiox emergent bypass system (Terumo, Tokyo, Japan). The mean+/-S.D. age was 56+/-18 (range, 14-85) years and 59 (64%) were male. The mean duration of PCPS was 90.9+/-126.0 h and that of cardiopulmonary resuscitation (CPR) was 51.1+/-27.8 min. The rate of weaning was 59/92 (64%) and the rate of survival to discharge was 39/92 (42%). The results indicated that the etiologic disease (myocarditis) and the cause of PCPS (cardiopulmonary arrest) are significantly correlated with weaning, whereas cardiopulmonary arrest and a shorter CPR duration (<60 min) are considerably correlated with survival. On the contrary, elderly patients (>75 years) have similar rates of weaning and survival compared with younger patients. PCPS provides an acceptable survival rate and outcome in patients with cardiac or respiratory failure. Prompt application and selection of patients with a specific disease (myocarditis) provides good results. It is also effective in elderly patients, providing hospital survival similar to that for younger patients.
LOE: 4
QUALITY: good
DIRECTION OF SUPPORT: supporting ABCE
COMMENTS: no report of industry sponsorship

22. Takahashi T, Harada M, et al. (2009). "The survey of out of cardiac arrest patients treated with pericutaneous cardiopulmonary support(PCPS) at Emergency Critical Care Center of the National Hospital Organization." IRYOU 63(7): 431-435.

Abstract in Japanese
LOE: 4
QUALITY: good
DIRECTION OF SUPPORT: supporting A, nerutoral BC
COMMENTS: no report of industry sponsorship

23. Tanno K, Itoh Y, Takeyama Y, Nara S, Mori K, Asai Y. Utstein style study of cardiopulmonary bypass after cardiac arrest. American Journal of Emergency Medicine 2008;26:649-54.

Objective: The aim of this study is to describe the effect emergency cardiopulmonary bypass (CPB) for resuscitation on the survival rate of patients. Methods: The study population was composed of persons 16 years or older who had out-of-hospital cardiac arrest and were transferred to the Sapporo Medical University Hospital from the scene between January 1, 2000, and September 30, 2004. Children younger than 16 years and persons who were dead were excluded. Data were collected according to the Utstein style. Survival rates and cerebral performance category were analyzed using χ^2 analysis for the patients with presumed cardiac etiology. Cardiopulmonary bypass was applied to patients who showed no response with standard advanced cardiac life support. The interval from collapse and other noncardiac etiologies were considered criteria for exclusion. Results: Of the 919 patient medical records reviewed, CPB was performed in 92 patients. Of the 919 patients, 398 were of presumed cardiac etiology (n = 66 for CPB), 48 patients survived, and 24 patients (n = 7 for CPB) had a good cerebral outcome (cerebral performance category score 1). With CPB, the rate of survival at 3 months increased significantly (22.7% vs 9.9%, $P < .05$), but the rate of good cerebral outcome (10.6% vs 5.1%, $P = .087$) showed a positive trend. Conclusion: The use of CPB for arrest patients was associated with reduced mortality. It did not increase good neurologic outcome significantly. Still, 7 cases with intact central nervous system would have been lost without CPB
LOE: 2
QUALITY: fair
DIRECTION OF SUPPORT: supporting C, neutoral D
COMMENTS: no report of industry sponsorship

24. Thiagarajan RR, Brogan TV, Scheurer MA, Laussen PC, Rycus PT, Bratton SL. Extracorporeal membrane oxygenation to support cardiopulmonary resuscitation in adults. Ann Thorac Surg 2009;87:778-85.

BACKGROUND: Extracorporeal membrane oxygenation (ECMO) to support cardiopulmonary resuscitation (CPR) has been shown to improve survival in children and adults. We describe outcomes after the use of ECMO to support

CPR (E-CPR) in adults using multiinstitutional data from the Extracorporeal Life Support Organization (ELSO) registry. METHODS: Patients greater than 18 years of age using ECMO to support CPR (E-CPR) during 1992 to 2007 were extracted from the ELSO registry and analyzed. RESULTS: Two hundred and ninety-seven (11% of 2,633 adult ECMO uses) reports of E-CPR use in 295 patients were analyzed. Median age was 52 years (interquartile range [IQR], 35, 64) and most patients had cardiac disease (n = 221; 75%). Survival to hospital discharge was 27%. Brain death occurred in 61 (28%) of nonsurvivors. In a multivariate logistic regression model, pre-ECMO factors including a diagnosis of acute myocarditis (odds ratio [OR]: 0.18; 95% confidence interval [CI]: 0.05 to 0.69) compared with noncardiac diagnoses and use of percutaneous cannulation technique (OR: 0.42; 95% CI: 0.21 to 0.87) lowered odds of mortality, whereas a lower pre-ECMO arterial blood partial pressure of oxygen (Pao(2)) less than 70 mm Hg (OR: 2.7; 95% CI: 1.21 to 6.07) compared with a Pao(2)of 149 mm Hg or greater increased odds of mortality. The need for renal replacement therapy during ECMO increased odds of mortality (OR: 2.41; 95% CI: 1.34 to 4.34). CONCLUSIONS: The use of E-CPR was associated with survival in 27% of adults with cardiac arrest facing imminent mortality. Further studies are warranted to evaluate and better define patients who may benefit from E-CPR.
LOE: 4
QUALITY: good
DIRECTION OF SUPPORT: neutral CE
COMMENTS: no report of industry sponsorship

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ORIGINAL ARTICLE
Cardiovascular Surgery

Early Induction of Hypothermia During Cardiac Arrest Improves Neurological Outcomes in Patients With Out-of-Hospital Cardiac Arrest Who Undergo Emergency Cardiopulmonary Bypass and Percutaneous Coronary Intervention

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Background: Therapeutic hypothermia for comatose survivors of out-of-hospital cardiac arrest has demonstrated neurological benefits. Although early cooling during cardiac arrest enhances efficacy in animal studies, few clinical studies are available.

Methods and Results: The 171 patients who failed to respond to conventional cardiopulmonary resuscitation were studied prospectively. Patients underwent emergency cardiopulmonary bypass (CPB) plus intra-aortic balloon pumping, with subsequent percutaneous coronary intervention (PCI) if needed. Mild hypothermia (34°C for 3 days) was induced during cardiac arrest or after return of spontaneous circulation. Of the 171 patients, 21 (12.3%) had a favorable neurological outcome at hospital discharge. An unadjusted rate of favorable outcome decreased in a stepwise fashion for increasing quartiles of collapse-to-34°C interval (P=0.016). An adjusted odds ratio for favorable outcome after collapse-to-CPB interval was 0.89 (95% confidence interval (CI) 0.82–0.97) and after CPB-to-34°C interval, 0.99 (95%CI 0.98–0.99) when collapse-to-34°C interval was divided into 2 components. Favorable neurological accuracy of a collapse-to-CPB interval at a cutoff of 55.5 min and CPB-to-34°C interval at a cutoff of 21.5 min was 85.4% and 89.5%, respectively.

Conclusions: Early attainment of a core temperature had neurological benefits for patients with out-of-hospital cardiac arrest who underwent CPB and PCI. (*Circ J* 2010; **74:** 77–85)

Key Words: Cardiac arrest; Cardiopulmonary bypass; Cardiopulmonary resuscitation; Extracorporeal circulation; Hypothermia

Despite decades of efforts to promote cardiopulmonary resuscitation (CPR) science and education, the neurologically intact survival rate for patients with out-of-hospital cardiac arrest remains low worldwide, averaging 6% or less.[1,2] Prompt bystander CPR and early defibrillation can significantly increase the chance of neurologically intact survival, but standard advanced life support (ALS) measures, such as tracheal intubation and pharmacological circulatory support, have not been shown to be beneficial to neurological outcome.[1–3] In 2 randomized clinical trials, induced hypothermia resulted in improved neurological outcomes,[4,5] and the 2005 CPR Guidelines recommended that unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest should be cooled to 32–34°C for 12–24 h when the initial rhythm was ventricular fibrillation (VF).[1,2] However, the number of patients who may benefit from therapeutic hypothermia is limited to approximately 8% of patients with out-of-hospital cardiac arrest.[1,4,6] In Japan, the SOS-KANTO study showed that a favorable neurological outcome at 30 days was extremely low in patients

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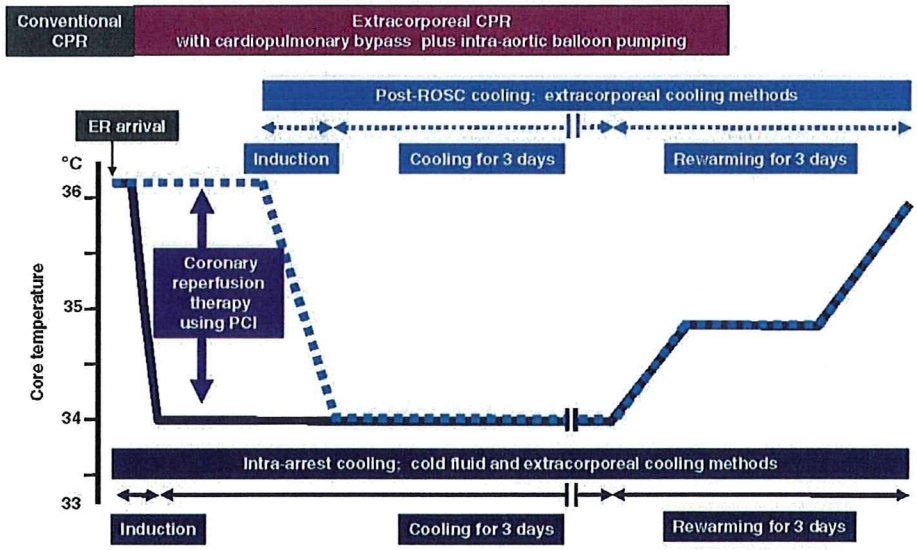

Figure 1. Protocol of extracorporeal cardiopulmonary resuscitation (CPR) for induction of hypothermia with percutaneous coronary intervention (PCI). After arrival at the emergency room (ER), extracorporeal CPR using emergency cardiopulmonary bypass plus intra-aortic balloon pumping was immediately performed. Subsequently, emergency coronary angiography with PCI was performed in cases of suspected acute coronary syndrome. The goal was to reach a target temperature of 34°C within 6 h in the post- return of spontaneous circulation (ROSC) cooling group (upper dotted part and dotted line), and within 30 min in the intra-arrest cooling group (lower gray part and gray line).

with out-of-hospital cardiac arrest who arrived at the emergency hospital in cardiac arrest.[7–9]

The 2005 CPR Guidelines recommended that extracorporeal CPR using emergency cardiopulmonary bypass (CPB) should be considered for patients with in-hospital cardiac arrest when the duration of the no-flow arrest was brief, and the condition leading to the cardiac arrest was reversible or amenable to heart transplantation or revascularization (Class IIb).[1,2] Chen et al showed that emergency CPB with normothermia produced a survival benefit over conventional CPR in patients with in-hospital cardiac arrest, although they did not identify neurological benefits.[10] Since 1994, we have performed extracorporeal CPR using emergency CPB plus intra-aortic balloon pumping, with subsequent percutaneous coronary intervention (PCI) if needed, on patients who arrive at the emergency room (ER) in cardiac arrest.[11,12] Our first study showed that extracorporeal CPR with normothermia is a useful perfusion method for cardiac resuscitation, although we did not obtain satisfactory effects for cerebral resuscitation.[11] Our next preliminary study indicated that extracorporeal CPR for induction of hypothermia after achievement of ROSC (post-ROSC cooling) may improve the chance of a favorable neurological outcome, with a low risk of complications.[12] Recent animal studies showed that induction of hypothermia during cardiac arrest (intra-arrest cooling) provided neurological benefits.[13–15] We therefore changed the timing of initiation of cooling and assessed whether early attainment of a target core temperature, inclusive of early implementation of extracorporeal CPR, had neurological benefits for patients with out-of-hospital cardiac arrest who failed to respond to conventional CPR.

Methods

Patients

We conducted a study of extracorporeal CPR for induction of hypothermia with PCI between November 2000 and December 2007 with the approval of the hospital research ethics board. Patients transported to the ER after out-of-hospital cardiac arrest were enrolled in this study when they met the following criteria: aged 18–74 years; cardiac arrest witnessed by bystanders; presumed cardiac etiology of cardiac arrest according to the Utstein style guidelines;[16] estimated time interval from collapse to paramedic's arrival at patient's side within 15 min; defibrillation using automated external defibrillator by bystander and/or emergency medical personnel; and persistent cardiac arrest on arrival at the ER. Exclusion criteria were a tympanic-membrane temperature below 30°C on arrival at the ER, successful ROSC within 10 min of arrival at the ER with conventional ALS; non-cardiac etiology of cardiac arrest; or pregnancy. Patients were also excluded if their families refused to give informed consent for participation in this study.

Procedures

Our treatment protocol of extracorporeal CPR for induction of hypothermia with PCI is shown in **Figure 1**. On arrival at the ER, the attending physicians assessed as soon as possible whether a patient was eligible for this study under conventional ALS.[1–3] Core temperature was immediately monitored by bladder temperature until a balloon flotation right-heart catheter was placed. CPB plus intra-aortic balloon pumping was initiated when ROSC could not be achieved within 10 min of arrival. The CPB system included a centrifugal pump (Capiox Sp pump controller, Sp-101, Terumo, Tokyo), a

hollow-fiber membrane oxygenator (Platinum cube NCVC 6000, Nipro, Osaka) and a heat exchanger unit (Heater-cooler system, MSH-15, Senko, Tokyo), and was primed with 600 ml lactated Ringer's solution with 2,000 U heparin. Flow of 100% oxygen though the oxygenator was adjusted to keep $PaCO_2$ between 35 and 45 mmHg. The CPB flow rate was kept at $\geq 70\ ml \cdot kg^{-1} \cdot min^{-1}$ until ROSC or 3 h after commencement of CPB. After implementation of CPB plus intra-aortic balloon pumping, emergency coronary angiography was performed during cardiac arrest in cases of suspected acute coronary syndrome (ACS). Subsequently, coronary reperfusion therapy using PCI during extracorporeal CPR was performed immediately if Thrombolysis In Myocardial Infarction (TIMI) grade 0, 1, or 2 flow[17] was observed in the ACS-related artery. When ROSC was achieved within 3 h of commencing CPB, the CPB flow rate was adjusted to maintain the mean arterial pressure between 90 and 120 mmHg and the pulmonary artery occlusive pressure between 15 and 20 mmHg. If hemodynamic instability persisted despite management with CPB plus intra-aortic balloon pumping, noradrenalin, dopamine, dobutamine and/or extracellular fluid infusion were administered as appropriate. Once the patient became hemodynamically stable with interruption of the CPB, CPB was weaned 24 h or more after cardiac arrest, and the intra-aortic balloon pump was removed 24 h later.

We used 2 procedures for the timing of initiation of cooling. The first method was post-ROSC cooling, used between November 2000 and November 2004. In the post-ROSC cooling group, comatose survivors who achieved ROSC within 3 h of implementing CPB were cooled to a target temperature of 34°C using the extracorporeal cooling method of CPB with a coil cooling device (KANEM or KTEK-3, as reported previously[12,18,19]). The goal was to reach the target temperature of 34°C within 5.5 h after implementing CPB. The target temperature was then maintained for 3 days using the extracorporeal cooling method, followed by gradual rewarming over at least 3 days (warming by 0.5°C every 12 h then maintained at 35°C for 24 h). During the period of hypothermia, the patient's condition was managed as reported previously.[12,18]

The second method was intra-arrest cooling, used between December 2004 and December 2007. In this group, patients were cooled to the target temperature of 34°C using an internal cooling method with rapid intravenous infusion of 2 L of lactated Ringer's solution at 4°C, and the extracorporeal cooling method with CPB primed with 600 ml of 4°C lactated Ringer's solution. The 500-ml bags of lactated Ringer's solution were stored in a refrigerator at 4°C before use. Until CPB implementation, 2 L of cold lactated Ringer's solution was infused using high-pressure intravenous infusion bags. The goal was to reach the target temperature of 34°C within 30 min after implementing CPB. In comatose survivors who achieved ROSC within 3 h of the implementation of CPB, the target temperature was maintained for 3 days using the extracorporeal cooling method. Management of the intra-arrest cooling group was otherwise the same for the post-ROSC cooling group.

Resuscitation attempts were documented by both paramedics and attending physicians according to the Utstein style guidelines.[15] In this study coronary angiographic findings were assessed by at least 3 interventional cardiologists. Data for individual patients were entered into a database by attending physicians, and were independently cross-checked twice by different investigators. Original data were made available to the data and safety monitoring committee for independent scrutiny.

Study Endpoints

The primary endpoint was a favorable neurological outcome at hospital discharge, defined according to the Glasgow-Pittsburgh cerebral-performance category of 1 (good performance) or 2 (moderate disability) on a 5-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).[16] The secondary endpoints were ROSC, survival for 7 days after cardiac arrest, survival to hospital discharge and a favorable neurological outcome at 1 year. ROSC was defined as palpitation of the carotid artery and the presence of systolic arterial pressure at the time of interruption of intra-aortic balloon pumping. Survival was defined as the Glasgow-Pittsburgh cerebral-performance category of 1, 2, 3, or 4.[16] Neurological outcomes were defined by physicians unconnected with this study.

Statistical Analysis

Estimates of the primary endpoint, a favorable neurological outcome at hospital discharge, were 10% for the post-ROSC cooling group and 15% for the intra-arrest cooling group from analyses of our previous studies of CPB.[12,18,19] Patients were divided into 4 groups using the quartiles of the collapse-to-34°C interval. Baseline characteristics were compared using the chi-square test for categorical variables, and the Kruskal-Wallis rank sum test for continuous variables, as appropriate. A multiple logistic regression analysis was done for independent predictors of the neurological outcome, including age, bystander CPR attempt, initial recorded cardiac arrest rhythm, and resuscitation-related time intervals. Finally we constructed a receiver-operating characteristic (ROC) curve to illustrate the various cutoff values of the collapse-to-CPB interval and the CPB-to-34°C interval as the 2 principal components of the collapse-to-34°C interval. A favorable neurological outcome was compared using the chi-square test among the 4 subsets of patients who were classified by those cutoff values. All analyses were performed using the SPSS software package (version 16.0 J SPSS; Chicago, IL, USA).

All authors had full access to the study data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

During the study period, 1,145 patients with an out-of-hospital cardiac arrest were transported to the ER. Of those, 974 patients were ineligible, so we included 171 (14.9%) patients who met the eligibility for this study: 102 had hypothermia induced after ROSC (post-ROSC cooling group), and 69 had hypothermia induced during cardiac arrest (intra-arrest cooling group).

The collapse-to-34°C interval ranged from 67 to 329 min, with a mean (±SD) of 204±96 min, median of 252 min, and the 25th and 75th percentile values of 94 and 286 min, respectively. Generally, the 4 groups of the patients according to the quartiles of the collapse-to-34°C interval had similar baseline characteristics, but significant differences were seen among the groups in the collapse-to-CPB interval and the CPB-to-34°C interval as principal components of the collapse-to-34°C interval (**Table**).

The primary outcome of a favorable neurological outcome at hospital discharge was seen in 21 (12.3%) of the 171 study patients. The favorable neurological outcome among all study patients decreased in stepwise fashion across the increasing quartiles of the collapse-to-34°C interval (quartile 1, 22.2% vs quartile 2, 14.6% vs quartile 3, 11.9% vs quartile 4, 0%, P=

Table. Baseline Characteristics of Patients According to the Quartiles of Collapse-to-34°C Interval

	Quartile 1 (<95 min) n=45	Quartile 2 (95–252 min) n=41	Quartile 3 (253–286 min) n=42	Quartile 4 (>286 min) n=43	P value
Age, years	59 (53–65)	62 (50–66)	57 (52–63)	59 (54–65)	0.90
Male	41 (91%)	34 (83%)	36 (86%)	37 (86%)	0.73
Location of cardiac arrest					0.27
Home or other residence	6 (13%)	7 (17%)	6 (14%)	13 (30%)	
Public, indoors	26 (58%)	23 (56%)	20 (48%)	16 (37%)	
Public, outdoors	13 (29%)	11 (27%)	16 (38%)	14 (33%)	
First findings at arrival of paramedics					
Gasping breathing	6 (13%)	3 (7%)	5 (12%)	3 (7%)	0.68
Initial cardiac rhythm					0.49
VF/pulseless VT	34 (76%)	35 (85%)	36 (86%)	38 (88%)	
PEA	6 (13%)	5 (12%)	3 (7%)	4 (9%)	
Asystole	5 (11%)	1 (2%)	3 (7%)	1 (2%)	
Cause of cardiac arrest					0.53
Acute coronary syndrome	35 (78%)	30 (73%)	32 (76%)	34 (79%)	
Cardiomyopathy	3 (7%)	0 (0%)	2 (5%)	3 (7%)	
Others	7 (16%)	11 (27%)	8 (19%)	6 (14%)	
Medical history					
Coronary heart disease	7 (16%)	7 (17%)	7 (17%)	7 (16%)	0.99
Hypertension	10 (22%)	8 (20%)	7 (17%)	8 (19%)	0.93
Heart failure	2 (4%)	0 (0%)	0 (0%)	1 (2%)	0.35
Diabetes	5 (11%)	6 (15%)	8 (19%)	7 (16%)	0.77
Prehospital treatment					
Bystander CPR	21 (47%)	24 (59%)	26 (61%)	23 (53%)	0.51
No. of defibrillations	4 (3–5)	4 (3–5)	4 (4–5)	4 (3–4)	0.66
Time interval (min)					
From collapse to call receipt	3 (3–4)	3 (3–5)	3 (3–4)	3 (2–4)	0.64
From call receipt to patient's side	7 (6–8)	7 (6–8)	7 (6–9)	7 (6–8)	0.77
From patient's side to arrival at emergency room	23 (20–27)	23 (20–30)	23 (21–29)	24 (22–28)	0.55
From collapse to implementation of CPB	63 (58–66)	68 (60–75)	63 (59–66)	66 (63–69)	0.0001
From implementation of CPB to attainment of 34°C	24 (20–27)	32 (28–184)	214 (203–217)	240 (227–250)	<0.0001
Angiographic data of ACS					
ACS-related artery	35	30	32	34	0.82
Left main artery	0/35 (0%)	1/30 (3%)	1/32 (3%)	1/34 (3%)	
Left anterior descending artery	18/35 (51%)	16/30 (53%)	18/32 (56%)	22/34 (65%)	
Left circumflex artery	5/35 (14%)	3/30 (10%)	6/32 (19%)	5/34 (15%)	
Right coronary artery	12/35 (34%)	10/30 (33%)	7/32 (22%)	8/34 (18%)	
TIMI flow grade of ACS-related artery					
Initial angiography; 0 or 1/2/3	28/3/4	23/6/1	22/4/6	28/3/3	0.40
TIMI flow grade 3 after PCI	27/31 (87%)	26/29 (90%)	21/26 (81%)	29/31 (94%)	0.68

Data are median (Interquartile range) or number (%). Calculations based on available data. The intra-arrest cooling accounted for 100% (45/45) of the Quartile 1 group and 58% (24/41) of the Quartile 2 group.
VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; CPR, cardiopulmonary resuscitation; CPB, cardiopulmonary bypass; ACS, acute coronary syndrome; TIMI, Thrombolysis In Myocardial Infarction; PCI, percutaneous coronary intervention.

0.016). This association remained significant among the subgroups of patients with bystander CPR attempt, VF/pulseless ventricular tachycardia as the initial cardiac rhythm, cardiac arrest because of ACS, and TIMI flow grade 3 after PCI (P<0.05, respectively) (**Figure 2**). The secondary endpoints of survival at 7 days after cardiac arrest, survival to hospital discharge, and a favorable neurological outcome at 1 year also decreased in stepwise fashion across the increasing quartiles of the collapse-to-34°C interval (P<0.05, respectively), although the 4 groups had a similar secondary endpoint of ROSC (**Figure 3**). In addition, no significant difference was seen among the 4 groups in the collapse-to-ROSC interval (median; quartile 1, 93 min vs quartile 2, 96 min vs quartile 3, 93 min vs quartile 4, 94 min, P=0.146).

A multiple logistic regression analysis for a favorable neurological outcome at hospital discharge showed that the collapse-to-34°C interval was an independent predictor, with an adjusted odds ratio (OR) of 0.99 (95% confidence interval (CI) 0.98–1.00, P=0.035). Another independent predictor was bystander CPR attempt (**Figure 4a**). When the collapse-to-CPB interval and the CPB-to-34°C interval as principal components of the collapse-to-34°C interval were entered into the model, both intervals were independent predictors of a favorable neurological outcome; an adjusted OR after

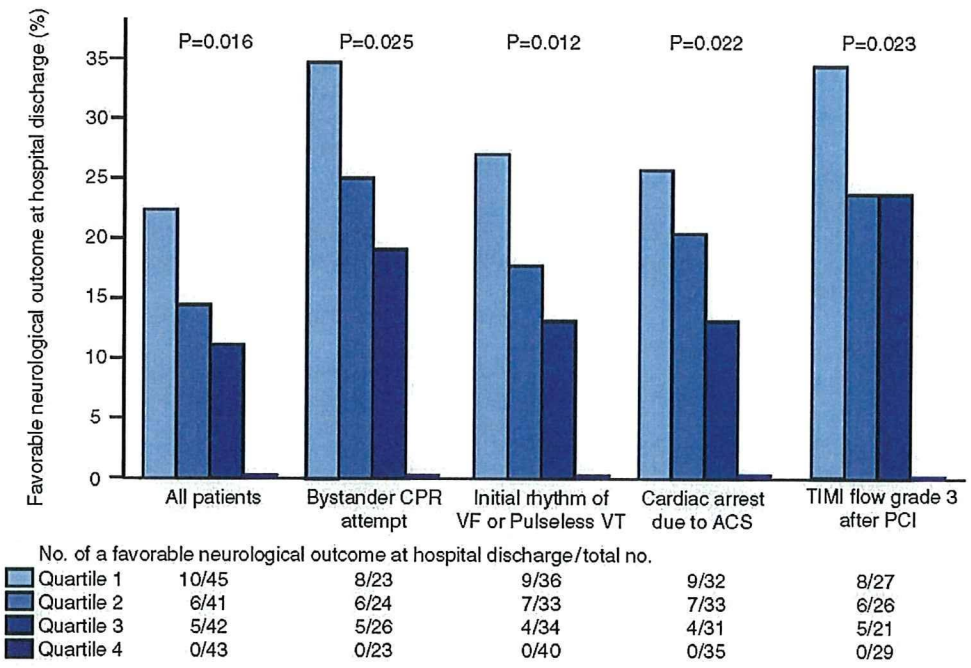

Figure 2. Association between the quartiles of the collapse-to-34°C interval and the frequency of a favorable neurological outcome at hospital discharge (primary endpoint) in all study patients and in selected subgroups. ACS, acute coronary syndrome; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

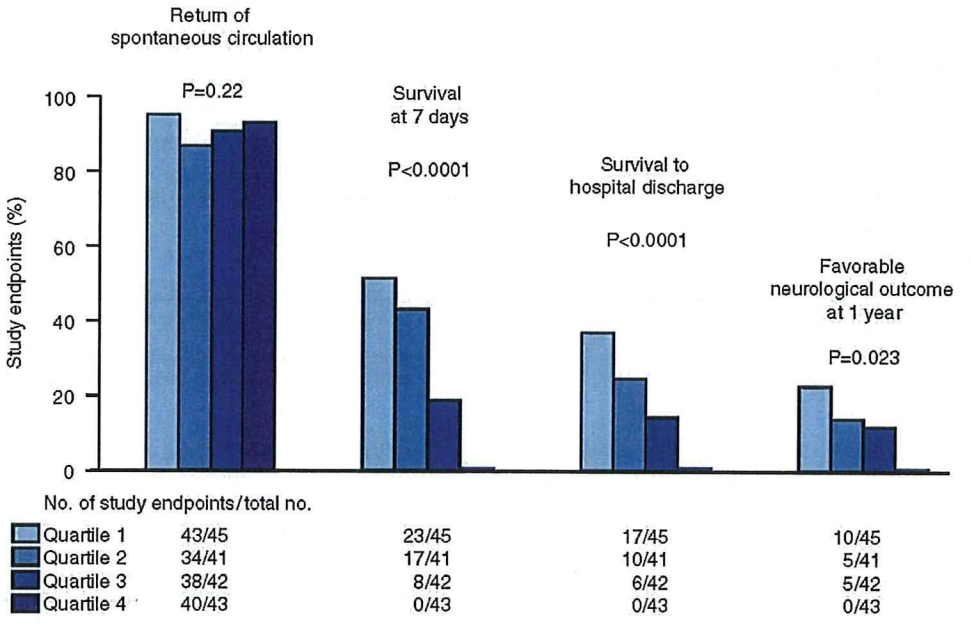

Figure 3. Association between the quartiles of the collapse-to-34°C interval and the frequencies of the secondary endpoints in all study patients.

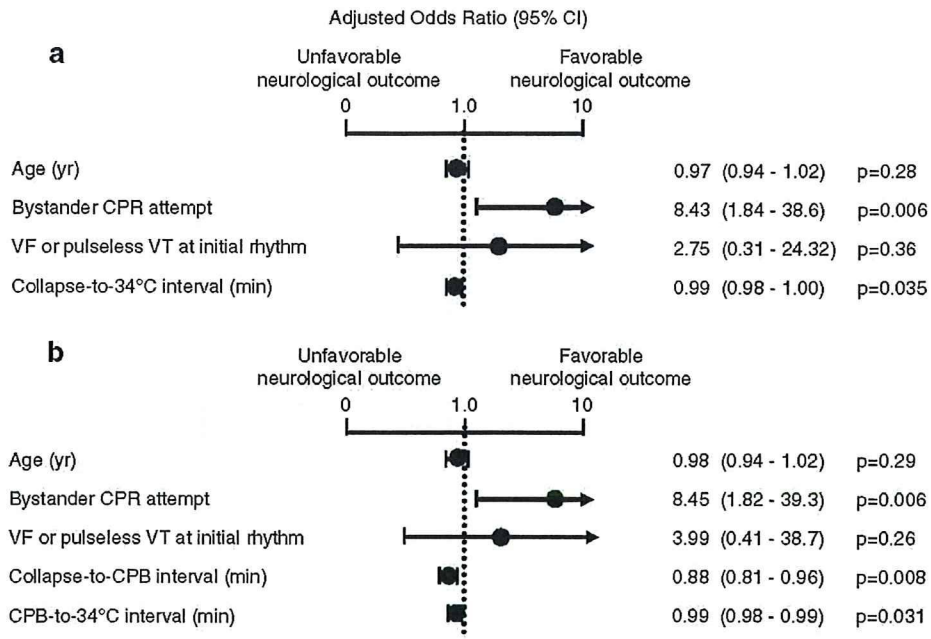

Figure 4. Adjusted odds ratios for a favorable neurological outcome at hospital discharge associated with selected factors, inclusive of the collapse-to-34°C interval (**a**) and the 2 principal components of the collapse-to-34°C interval (the collapse-to-CPB interval and the CPB-to-34°C interval) (**b**). CI, confidence interval; CPB, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia.

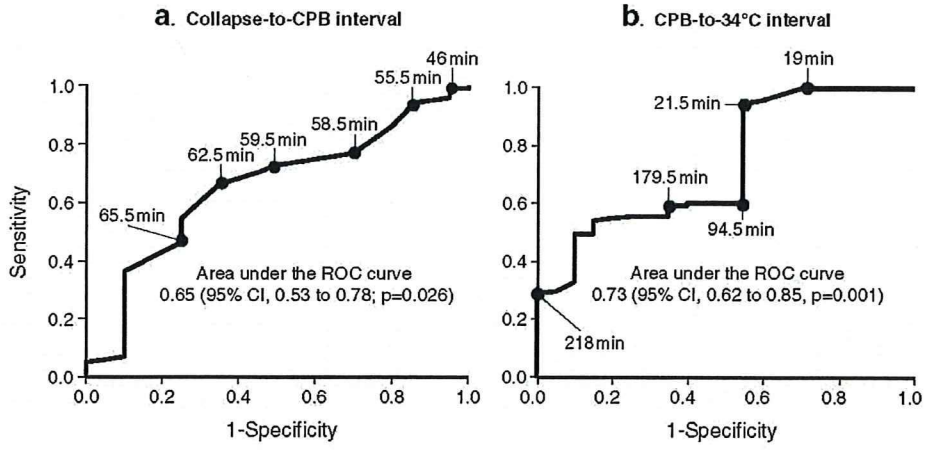

Figure 5. Receiver-operating-characteristics (ROC) curves for various cutoff levels of the collapse-to-CPB interval (**a**) and the CPB-to-34°C interval (**b**) to differentiate a favorable neurological outcome and an unfavorable neurological outcome at hospital discharge. CPB, cardiopulmonary bypass.

the collapse-to-CPB interval was 0.88 (95%CI 0.81–0.96) and after the CPB-to-34°C interval, 0.99 (95%CI 0.98–0.99) (**Figure 4b**). In the subgroup of patients with ACS, the results did not change when coronary angiography findings were included in the multiple logistic-regression analyses.

The area under the ROC curve of the collapse-to-CPB interval was 0.65 (95%CI 0.53–0.78; P=0.026), and the collapse-to-CPB interval cutoff value of 55.5 min had the highest combined sensitivity and specificity, with an accuracy of 85.4% for identification of a favorable neurological

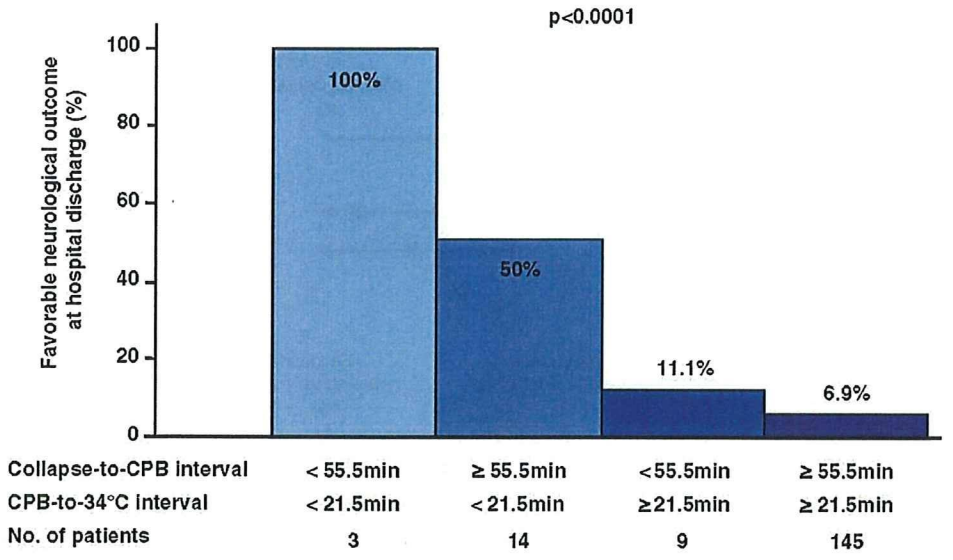

Figure 6. Frequencies of a favorable neurological outcome at hospital discharge among the 4 subsets of patients who were classified by the 2 cutoff values (collapse-to-CPB interval of 55.5 min and CPB-to-34°C interval of 21.5 min). CPB, cardiopulmonary bypass.

outcome. The area under the ROC curve of the CPB-to-34°C interval was 0.73 (95%CI 0.62–0.85, P=0.001), and the CPB-to-34°C interval cutoff value of 21.5 min had the highest combined sensitivity and specificity, with an accuracy of 89.5% (**Figure 5**). A significant difference was seen in the favorable neurological outcome among the 4 subsets of patients who were classified according to these cutoff values (P=0.0001) (**Figure 6**).

Discussion

This study shows that early attainment of a core temperature of 34°C during extracorporeal CPR with PCI has neurological benefits for patients with out-of-hospital cardiac arrest who fail to respond to conventional CPR. The unadjusted rate of a favorable neurological outcome at hospital discharge decreased in a stepwise fashion with the increasing quartiles of the collapse-to-34°C interval and this association remained significant in subgroups of patients (**Figure 2**). A multiple logistic regression analysis demonstrated that each collapse-to-CPB interval and CPB-to-34°C interval as principal components of the collapse-to-34°C interval was an independent predictor for a favorable neurological outcome at hospital discharge (**Figure 4b**). Each cutoff value for identification of a favorable neurological outcome was 55.5 min in the collapse-to-CPB interval and 21.5 min in the CPB-to-34°C interval (**Figure 5**). A significant difference was seen in the favorable neurological outcome among the 4 subsets of patients who were classified by those cutoff values (**Figure 6**).

Although several clinical studies of emergency CPB with normothermia for patients with cardiac arrest have been conducted,[11,20–25] there have been few clinical studies of emergency CPB for induction of hypothermia.[12] Martin et al,[20] Younger et al[21] and our previous study[11] showed no benefit of emergency CPB with normothermia for neurological outcomes in patients who arrived at the ER in cardiac arrest, with the exception of cardiac arrest associated with accidental hypothermia or drug intoxication. On the other hand, Chen et al,[22] Hase et al,[23] and Kano et al[24] found that early implementation of emergency CPB with normothermia (<45 min[23] or <60 min[22,24] after cardiac arrest) was associated with better neurological outcomes. In this study, we showed that the optimal cutoff point for the collapse-to-CPB interval regarding a favorable neurological outcome at hospital discharge is 55.5 min. However, we consider it a most difficult task to implement CPB within 55.5 min after out-of-hospital cardiac arrest, because the recorded collapse-to-CPB intervals ranged from 47 to 94 min, with a mean (±SD) of 64.4±6.7 min and a median (interquartile range) of 65 (60–68) min. Such results suggest that extracorporeal CPR strategies will need to include some additional treatment for patients undergoing prolonged conventional CPR. Our preliminary study raised the possibility that extracorporeal CPR for induction of hypothermia after ROSC (post-ROSC cooling) might improve neurological outcomes.[12] Recent animal studies showed that induction of hypothermia during cardiac arrest (intra-arrest cooling) enhanced the neurological benefits, and the sooner cooling was initiated in cardiac arrest, the better the outcome.[13–15] Using a mouse model of VF cardiac arrest (no-flow) for 8 min, Abella et al showed that early induction of intra-arrest cooling after 8 min of VF significantly increased the 72-h survival rate compared with either delayed induction of post-ROSC cooling after 30 min of VF or normothermic resuscitation.[13] Using a canine model of VF cardiac arrest (no-flow) for 3 min, followed by 7 min of CPR, and 30 min of ALS, Nozari et al showed that induction of intra-arrest cooling after 20 min of VF significantly increased the 96-h intact survival rate compared with normothermic resuscitation. Moreover, they showed that early induction of intra-arrest cooling after 10 min of VF significantly increased the 96-h intact survival

rate compared with delayed induction of intra-arrest cooling after 20 min of VF.[14,15] Although these results indicate that induction of intra-arrest cooling should begin within 20 min of cardiac arrest, we consider that there are substantial differences between the animal and the clinical studies in the time interval from induction of cooling to attainment of the target core temperature. In the animal studies, the target temperature was attained within 10 min after initiation of cooling using either an external or internal cooling method,[13–15] whereas the clinical studies of therapeutic hypothermia have shown that external cooling methods require several hours to attain the target temperature, and that rapid infusion of cold fluids (30 ml/kg or 2 L) significantly reduces the core temperature, although in those particular cases the target temperature of 33–34°C was not reached.[26–29]

Although mild hypothermia reduces the cerebral metabolic rate of oxygen consumption, and is thought to suppress many of the chemical reactions associated with reperfusion injury, the adverse effects include coagulopathy, cardiac dysrhythmias, impaired cardiac function, and increased susceptibility to infection. The prevalence and severity of these adverse effects is proportional to the depth and duration of cooling.[1,2,6,29] Animal studies of intra-arrest cooling have shown that a target temperature ≤34°C and cooling duration ≤12 h produces better outcomes than normothermic resuscitation (30°C for 1 h in Abella's study,[13] 27°C or 34°C for 12 h in Nozari's studies[14,15]). Using a porcine model of VF cardiac arrest (no-flow) of 8 min, Boddicker et al showed that pre-existing hypothermia of 30°C or 33°C facilitated significantly improved resuscitation outcomes in comparison with normothermic resuscitation, but that a temperature of 35°C was not beneficial to the resuscitation outcome.[30] Wu et al showed that profound hypothermia (10–15°C for 1 h), followed by mild hypothermia (34°C for 36 h) produced a better intact survival rate than normothermic resuscitation or profound hypothermia (10–15°C for 1 h), followed by mild hypothermia (34°C for 12 h) in a canine model of hemorrhagic cardiac arrest.[31] Gunn et al reported that delayed onset brain edema following 30 min of cerebral ischemia was abolished by prolonged (3-day) hypothermia.[32] In the present study, mild hypothermia (34°C) was maintained for 3 days because we considered that the patients who arrived at the ER in cardiac arrest after out-of-hospital cardiac arrest presented with more severe conditions for resuscitation than those who achieved ROSC before arrival at the ER.

In this study, the majority of patients who achieved ROSC by extracorporeal CPR died of myocardial dysfunction during the cooling stage, which suggests that cardiac function during the cooling stage after ROSC was worse in this study than in the animal studies. Several reasons might account for the low neurologically intact survival rate. There was a significant difference in the cause of the cardiac arrest between this study and the animal studies. In this study, ACS accounted for approximately 80% of cases of cardiac arrest, although coronary reperfusion therapy using PCI during cardiac arrest successfully restored antegrade coronary flow (TIMI flow grade 3) in 88% of the patients and the unadjusted rate of a favorable neurological outcome at hospital discharge decreased in a stepwise fashion with the increasing quartiles of the collapse-to-34°C interval in the subgroup of patients who achieved TIMI flow grade 3 after PCI. Knafelj et al reported that early PCI with mild hypothermia was superior to early PCI without hypothermia in comatose survivors after cardiac arrest because of ST-elevation myocardial infarction, in terms of survival benefit.[33] These findings suggest that early induction of hypothermia and PCI protects myocardium from post-cardiac arrest syndrome in patients with out-of-hospital cardiac arrest because of ACS. It is possible that the core temperature of 34°C and/or the cooling duration of 3 days used in the present study do not represent optimum hypothermia. Further clinical studies are needed to determine the optimum target temperature and cooling duration for patients who arrive at the ER in cardiac arrest, and who are treated with extracorporeal CPR for induction of hypothermia and PCI. An ethical issue of this study was withdrawal of CPB, which is an emotionally complex decision for family and staff. We considered the following 4 factors to be associated with an irreparable state: asystole, apnea, absence of papillary response to light and papillary dilatation. When those factors continued for 3 h after commencement of CPB or appeared as a result of aggravation after admission to hospital, we asked the family for informed consent to withdrawal of CPB. Most of families agreed, but it took almost 3 days after commencement of CPB.

Study Limitations

This was neither a randomized controlled trial nor a multicenter study. Although it is difficult to conduct a randomized controlled trial of extracorporeal CPR for patients with out-of-hospital cardiac arrest in Japan, we have begun a multicenter observational study of extracorporeal CPR with hypothermia (UMIN000001403).[34]

This study period extended past the limit of the 2005 CPR Guidelines; however, we considered this had no serious effects on the study patients who failed to respond to conventional CPR. The use of extracorporeal CPR was limited to the hospital setting and was too invasive for use in most hospitals, but the SOS-KANTO study has shown that the neurological intact survival rate is extremely low in patients with witnessed out-of-hospital cardiac arrest who arrive at hospital in cardiac arrest.[7,8] Each year, out-of-hospital cardiac arrest occurs in approximately 100,000 people in Japan,[35] approximately 5,000 of whom would meet our criteria for extracorporeal CPR for induction of hypothermia. Finally, cooling was initiated after arrival at the ER, but if intravenous infusion of large-volume, ice-cold fluids was used for the pre-hospital induction of intra-arrest cooling, a favorable neurological outcome might ensue.

Conclusions

Early attainment of a core temperature of 34°C during cardiac arrest had neurological benefits for patients with out-of-hospital cardiac arrest who underwent CPB and PCI.

Acknowledgments

We thank all the bystanders who provided basic resuscitation and/or automated external defibrillation, and the paramedics, emergency medical technicians, nurses and physicians who participated in this study.

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Disclosures

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厚生労働科学研究費　野々木・坂本班

J-PULSE・SAVE-J　合同公開報告会

新しい循環器救急システムの実践報告

日時：平成 22 年 2 月 23 日（火）

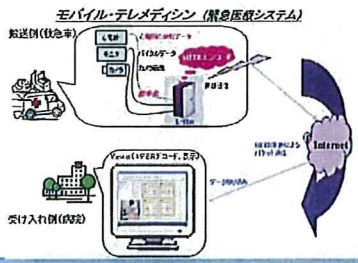
13：00　～　17：00

場所：日本大学カザルスホール

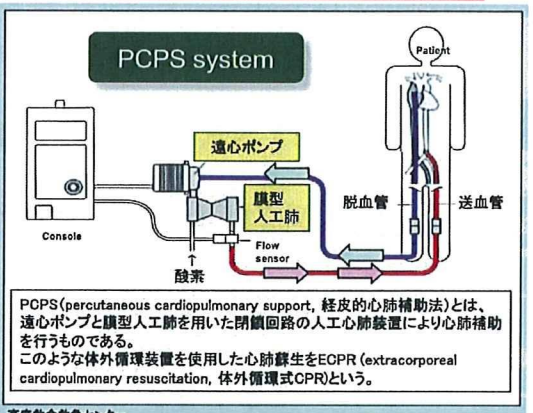
平成１９年から、３年間の厚生労働省科学研究の成果報告会を開催する運びとなりました。急性心筋梗塞や脳卒中の超急性期医療の確立のため、早期治療を開始するための啓発方法、第３世代携帯電話による汎用性インターネットを用いて、　１２誘導心電図やバイタルサイン、動画を伝送するモバイルテレメディシン、搬送方法、超重症例への抗不整脈薬や補助循環、低体温療法、院内心停止への対策など、救急疾患の早期診療に効果をあげてまいりました。
2 つの研究班で救急に関する共通の取り組みがあり、国際発信を含め救急システムへの展開において共同作業が期待されるため、合同で皆様方に広くご報告できる機会を設けさせていただきました。
ご関心のある皆様方に広くご参集いただき、今後の救急医療の展望について御意見交換をいただければ幸いに存じます。

国立循環器病センター心臓血管内科　野々木　宏
帝京大学救急医学講座　坂本　哲也
駿河台日本大学病院 循環器科　心肺蘇生・救急心血管治療　長尾　建
問い合わせ先：06-6833-5012　内線 2233　　野々木部長室　秘書　林久美子

（ｱｸｾｽ http://www.nu-casalshall.com/）



The ECPR Japanese Network



PCPS(percutaneous cardiopulmonary support, 経皮的心肺補助法)とは、遠心ポンプと膜型人工肺を用いた閉鎖回路の人工心肺装置により心肺補助を行うものである。
このような体外循環装置を使用した心肺蘇生をECPR (extracorporeal cardiopulmonary resuscitation, 体外循環式CPR)という。

SAVE-J study group

田原良雄　:横浜市立大学附属市民総合医療センター 高度救命救急センター
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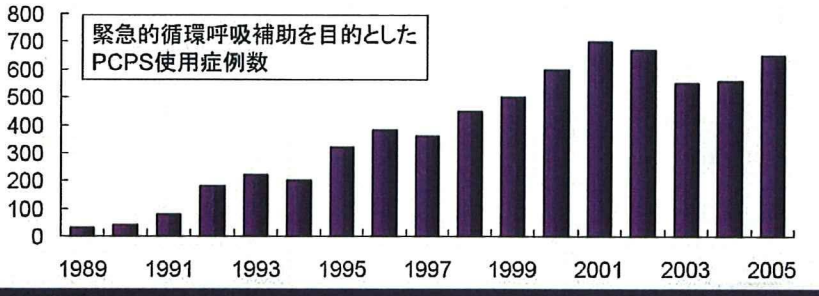
背景

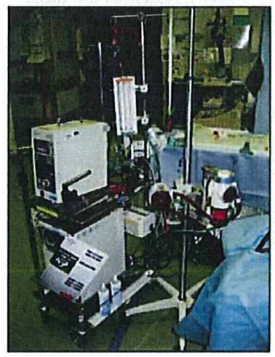
- 近年、本邦におけるPCPSの使用頻度は増加傾向にある。
- 特に通常の二次救命処置に反応しないCPAに対するPCPSを用いたECPRが普及しつつある。

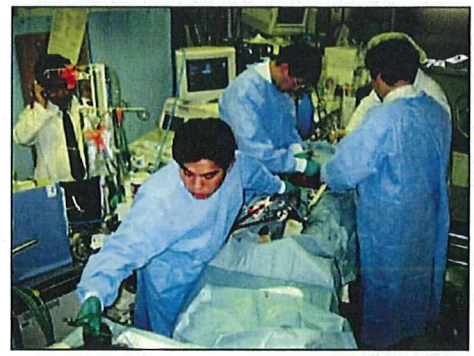


http://www2.convention.co.jp/pcps/
Japanese society of Percutaneous Cardio-Pulmonary Support

背景

- 迅速な救命処置が行われたにもかかわらず蘇生できない院外CPAに対するECPRによる救命例も散見されるが、ECPRの有用性に関して世界的合意を検討するだけの十分な報告がなかった。





方法

院外CPAに対するECPRの効果を検討するために以下の3点を検討

(1) 1983年から2007年までのECPRに関する和文報告を検討

(2) 全国の救命救急センターおよび大学病院の救急部に対して2007年度の院外CPAに対するECPRに関するアンケート調査による検討

(3) 5施設による2006年度の院外CPAに対するECPR50例に関する後ろ向き診療録調査に基づく前向き調査の検討

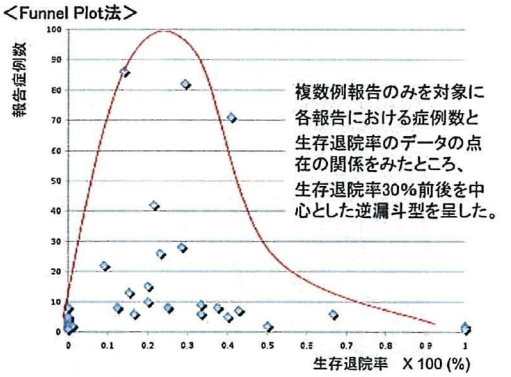
(1) 和文報告

	No of articles	No of cases	Survive	Mean	SE	Lower	Upper
All cases	54	991	288				
生存退院率				29.1%	1.4%	26.2%	31.9%

期間:1983年1月～2007年7月
院外CPAに対するECPR

一例報告43例を除く、
複数例報告62報、1239例中、
退院時予後の記載のある例を
対象とした。

<Funnel Plot法>

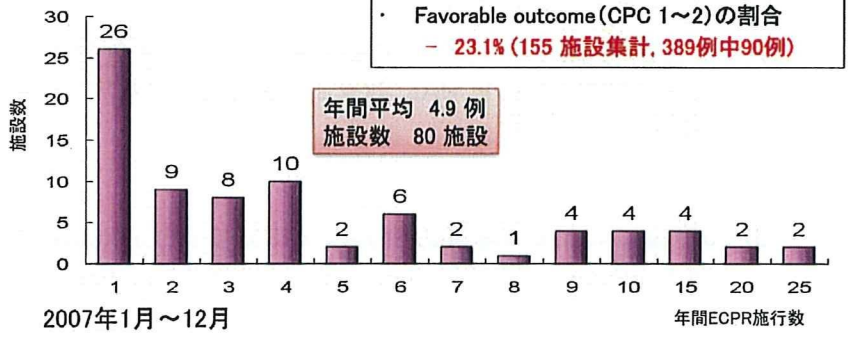


複数例報告のみを対象に
各報告における症例数と
生存退院率のデータの点
在の関係をみたところ、
生存退院率30%前後を中
心とした逆漏斗型を呈した。

(2) アンケート調査

- 全国救命救急センター、大学病院救急部
  - 255 施設
- 回答率
  - 60.8% (155/255 施設)
- ECPR施行施設
  - 51.6% (80/155 施設)
- Favorable outcome(CPC 1～2)の割合
  - 23.1% (155 施設集計, 389例中90例)

<年間ECPR施行数の度数分布>



年間平均 4.9 例
施設数 80 施設

2007年1月～12月

(3) 後ろ向き診療録調査

・ 研究者施設	5 施設
・ 調査期間	2006年 1月～12月
・ 院外CPA症例	1220 例
・ ECPR 例	50 例 (4.1 %)
一生存退院率	27.1%
一社会復帰率	12.5 %
・ 前向き研究の適格基準	20 例 (1.6 %)
一生存退院率	30.0 %
一社会復帰率	10.0 %

これらの検討の結果、通常の二次救命処置に反応しない院外VF-CPAに対するECPRの有用性を前向き観察研究として2008年10月より開始した。

SAVE-J

Study of
Advanced life support for
Ventricular fibrillation with
Extracorporeal circulation in
Japan

http://www.save-j.net/

The Japanese scientific research group under the Ministry of Health, Labor and Welfare for extracorporeal cardiopulmonary resuscitation.

SAVE-J study

＜対象患者＞
（適格基準）
以下の全てを満たす院外CPA患者を対象とする。
1) 確認できた初回心電図が心室細動または無脈性心室頻拍
2) 病院到着時心停止。病院到着までの間の自己心拍再開の有無は問わない
3) 119番通報あるいは心停止から病院（本研究参加施設）到着まで45分以内
4) 病院到着後（医師が患者に接触後）15分間心停止が持続している（1分以上の自己心拍再開がない）
5) 目撃者の有無は問わない
6) バイスタンダーによるCPRの有無は問わない

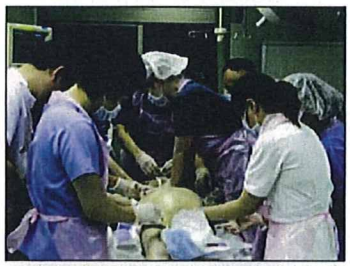
（除外基準）
以下のいずれかに該当する患者は、本研究に組み入れない。
1) 年齢20歳未満または75歳以上
2) 発症前の日常生活動作（ADL: activities of daily livings）が不良
3) 原疾患が非心原性（外傷、薬物中毒など外因性、一次性頭蓋内疾患、導入前に診断ができている急性大動脈解離、末期癌など）
4) 深部体温30℃未満
5) 代諾者の同意が得られない

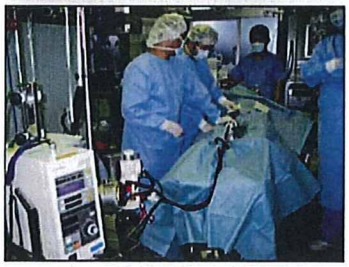
研究デザイン

- 前向き観察研究
  （非ランダム化比較対照試験）
  - ■ 非ECPR群施設
  - ■ ECPR群施設

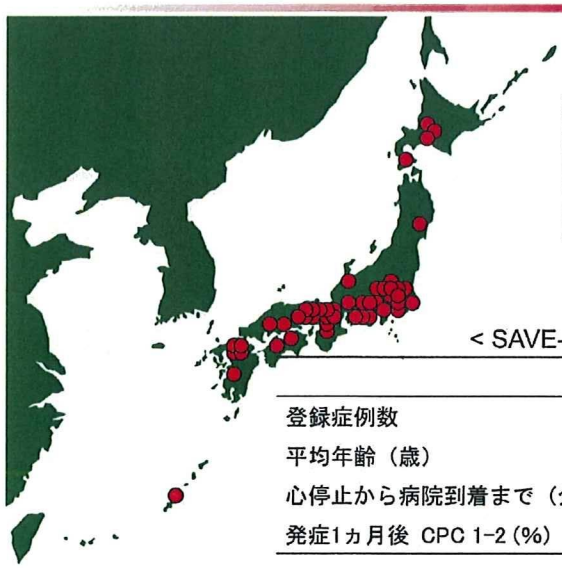
※ 低体温療法およびSTEMIに対するPCIは両群共通

- エンドポイント
  発症1ヵ月後のグラスゴー・ピッツバーグ脳機能全身機能カテゴリーにおける機能良好および中等度障害（CPC1または2）の合計数の割合





SAVE-J study early data
[2008年10月～2009年3月]



参加施設数	56
ECPR 施設数	30
非ECPR 施設数	26

< SAVE-J early data >

	ECPR	Non-ECPR
登録症例数	35	7
平均年齢（歳）	55	58
心停止から病院到着まで（分）	29	25
発症1ヵ月後 CPC 1-2 (%)	21	0

J-PULSE・SAVE-J　合同公開報告会（2010年2月23日，東京）

J-PULSE・SAVE-J合同委員会のメンバー（2010年3月3日，広島）

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告書

心肺停止患者に対する心肺補助装置等を用いた高度救命処置の効果と費用に関する多施設共同研究　中間解析

分担研究者　浅井康文　札幌医科大学附属病院高度救命救急センター　教授
分担研究者　長尾　建　駿河台日本大学病院 循環器 心肺蘇生 救急心血管治療　教授

研究要旨

院外心停止症例を対象としたPCPSを用いた心肺蘇生が，アウトカムを改善することを検証することを目的とした前向き臨床研究の中間解析を行った。主要アウトカムは，発症1カ月後のCerebral Performance Categories（CPC）とし，各群のfavorable outcome（CPC1，2）の割合を，カイ二乗検定，またはフィッシャーの正確確率検定にて比較した。また，PCPSの合併症，コストに関しても中間集計を行った。

中間解析の結果，PCPS群のfavorable outcomeの割合は非PCPS群に比べて良好であり，PCPSが通常の二次救命処置のみより予後を良くすることが示唆された。しかしながら，今回の解析は2010年3月末日時点で登録されたデータに基づくものであり，特に非PCPS群の適格症例を全て収集できていないことによるサンプルバイアスが否定できない。またPCPS群で予後不明例が10例あるため，今回の結果からPCPSの有効性を結論づけることはできない。最終解析に際しては，参加施設に適格規準の周知を徹底するとともに，引き続き症例登録を支援する必要がある。また長期予後を追跡し，PCPSの有効性に関して更なる検証が必要である。

【研究協力者】
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A.　研究目的

院外心肺停止（CPAOA）症例に対するPCPSを用いた心肺蘇生法が，標準的な心二次救命処置のみに比べてアウトカムを改善することを検証する。

B.　研究方法

B.1. デザイン

前向き比較対照観察研究。日常診療において適格規準に合致する症例にPCPSを積極的に導入している施設をPCPS群に，積極的に導入していない施設（偶発性低体温症や薬物中毒，20歳未満のCPAOA等に対する積極的な導入は含まない）を非PCPS群とした。

B.2. 対象

B.2.1. 適格規準

2008年9月8日から2009年12月31日までに研究参加施設に来院した患者のうち，以下の全てを満たす患者を対象とした。

1）確認できた初回心電図が心室細動（ventricular fibrillation）または無脈性心室頻拍（pulseless ventricular tachycardia）（以下併せてVF）
2）病院到着時心停止。病院到着までの間の自己心拍再開（以下ROSC：recovery of spontaneous circulation）の有無は問わない
3）119番通報あるいは心停止から病院（本研究参加施設）到着まで45分以内