Objective

To investigate the effects of target core temperature on neurological outcome of cardiac arrest patients treated with therapeutic hypothermia.

Methods

We conducted a multi-center retrospective study at 16 institutions to evaluate the effect of therapeutic hypothermia on out-of-hospital cardiac arrest between January 2005 and December 2008.
The study committee entrusted each hospital with the timing of cooling, cooling methods, target temperature, duration, and rewarming rate.

Methods (cont'd)

Study Population

Patients with therapeutic hypothermia after cardiac arrest from 2005 to 2008 in each hospitals.

Inclusion Criteria

- Adult patients who remained unconscious after resuscitation from out-of-hospital cardiac arrest.
- Presented the stable hemodynamics with drug treatments or mechanical supporting system including IABP or PCPS.

Exclusion Criteria

- Patients with pregnancy, acute aortic dissection, pulmonary thromboembolism, drug poisoning, and

Methods (cont'd)

Analysis

- Patients were divided into the L group (32~34°C) and the M group (34~35°C) according to target core temperature.

- Neurological outcome was compared at hospital discharge. A favorable outcome was defined as a Cerebral Performance Category (CPC) of 1-2.

Results

1. **A total of 281 patients were enrolled. The median interval from collapse to return of spontaneous circulation was 18 (12-29) minutes.**
2. **Between the L group (n=35) and the M group (n=246), the rates of survivors (74% vs. 79%) and favorable outcomes (51% vs. 57%) were not statistically different.**
3. **As compared with the M group, the L group had significantly higher rates of inadequately controlled core temperature (60% vs. 35%, p=0.005), and side effects of hypothermia (50% vs. 26%, p=0.0079).**

Table 1. Baseline Characteristics

Number of patients	281
Age (years)	60 (51-68)
Male (%)	235 (84%)
Witnessed cardiac arrest (%)	247 (88%)
Performed bystander CPR (%)	145 (52%)
Time from collapse to ROSC (min)	18 (12-29)
Initial arrest rhythm: VF/VT (%)	226 (80%)

Table 2. Method of Hypothermia

Cooling methods	
- Surface cooling (%)	159 (57%)
- Extracorporeal circulation (%)	102 (36%)
- Intravascular catheter (%)	8 (3%)
- Infusion of ice-cold fluid (%)	135 (48%)
Duration of cooling (hours)	27 (24-48)
Target core temperature (°C)	
- 32 ~ 33.9°C	35 (12%)
- 34 ~ 35°C	246 (88%)

Table 3. Comparison of Outcome

	L group	M group	*p* Value
Number of patients	35	246	
Age (years)	52 (45-61)	61 (52-69)	0.0014
Target temperature (°C)	33 (33-33)	34 (34-34)	<0.0001
Duration of cooling (hrs)	49 (26-51)	26 (24-46)	0.0009
Surface cooling (%)	25 (71%)	134 (54%)	0.0688
Survival (%)	26 (74%)	195 (79%)	0.5110
Favorable outcome (%)	18 (51%)	139 (57%)	0.5897

Table 4. Side Effects of Hypothermia

	L group	M group	*p* Value
Inadequately controlled core temperature (%)	21 (60%)	82 (35%)	0.0050
Over-cooling (%)	14 (40%)	53 (22%)	0.0326
Side effects (%)	17 (50%)	64 (26%)	0.0079
- Arrhythmia	6 (17%)	14 (6%)	0.0256
- Infection	6 (17%)	43 (17%)	0.9608
- Blood transfusion	7 (20%)	26 (11%)	0.1541

Table 4 (cont'd) Side Effects of Hypothermia

Definition

1) Inadequately controlled core temperature:
Core temperature exceeds target temperature ± 0.5 °C

2) Over-cooling:
Core temperature decreases more than 0.5 °C from target temperature

Conclusions

1. **Target core temperature did not affect neurological outcome of cardiac arrest patients.**
2. **The lower target core temperature might cause increase of side effects.**
3. **To control core temperature adequately, further studies of cooling methods and managements are needed.**

Institutions Participated in the J-PULSE-Hypo Investigators

- Hiroshima Shimin Hospital
- Osaka Police Hospital
- Sumitomo Hospital
- Osaka City Medical Center
- Saga University Hospital
- Nihon University Surugadai Hospital
- Kitazato University
- Yamaguchi University Hospital
- Kokura Memorial Hospital
- Sapporo City University Hospital
- Kobe City Medical Center General Hospital
- Kagawa University Hospital
- Yokohama City Hospital
- National Cardiovascular Center
- Osaka Saiseikai Senri Hospital
- Osaka Mishima Emergency Critical Care Center

For information regarding this presentation:

Shunji Kasaoka, MD

AMEC3, Yamaguchi University Hospital

1-1-1 Minami-Kogushi, Ube 755-8505, Japan

E-mail: skasa@yamaguchi-u.ac.jp

Impact of Duration of Cooling in Mild Therapeutic Hypothermia on Comatose Survivors of Out-of-Hospital Cardiac Arrest: J-PULSE-Hypo Registry

Eisuke Kagawa, Masaharu Ishihara, Tatsuya Maruhashi, Naohiro Yonemoto, Hiroyuki Yokoyama, Ken Nagao, Hiroshi Nonogi, and J-PULSE-Hypo investigators

Disclosure

Eisuke Kagawa, None; Masaharu Ishihara, None; Tatsuya Maruhashi, None; Naohiro Yonemoto, None; Hiroyuki Yokoyama, None; Ken Nagao, None; Hiroshi Nonogi, a grant from the Ministry of Health, Labor and Welfare in Japan, significant, research grant.

Background

Mild therapeutic hypothermia (MTH) has a neuroprotective effect and results in improved survival and neurological outcome in comatose survivors of out-of-hospital cardiac arrest.

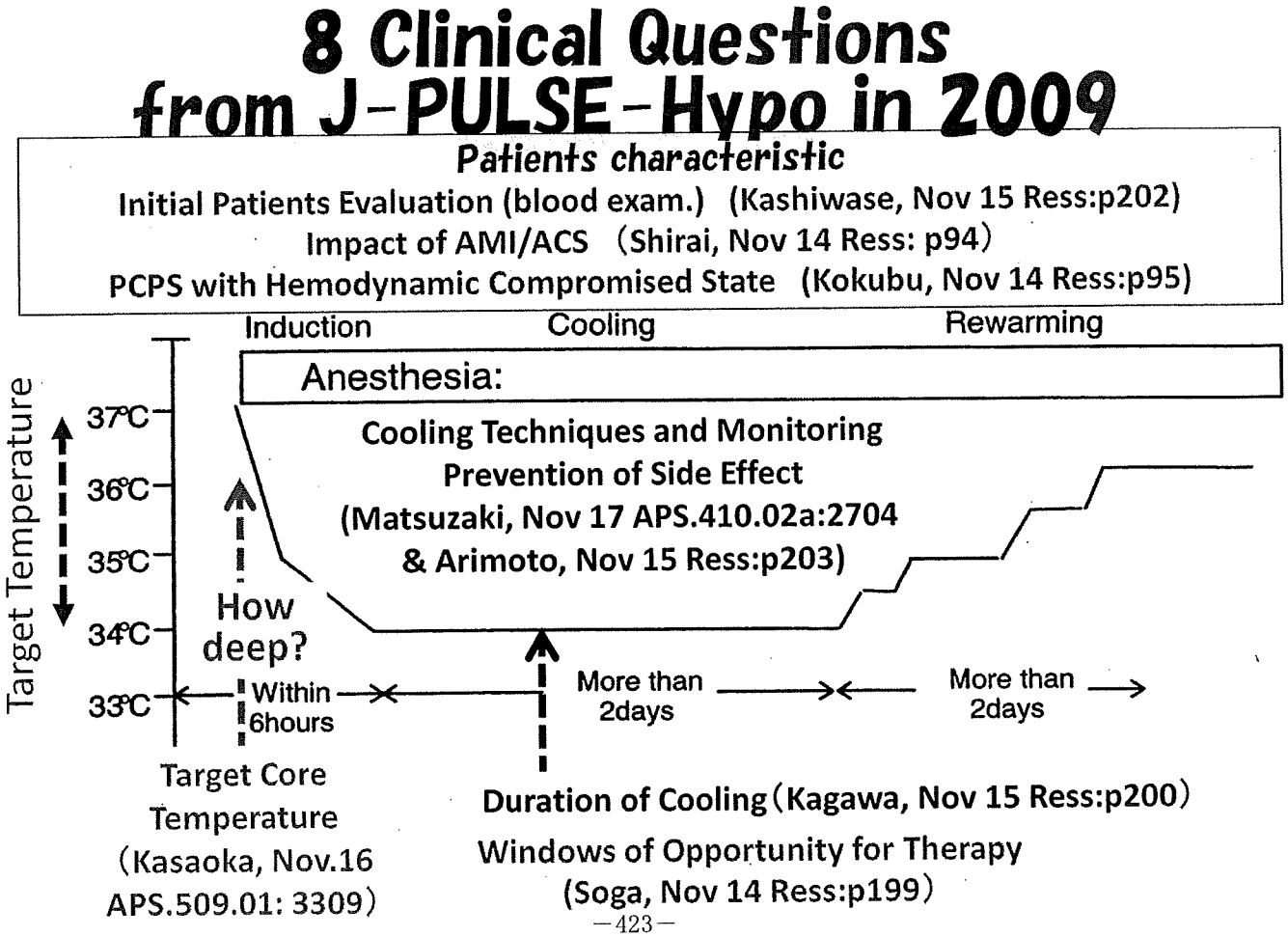
However, the optimal duration of cooling in MTH is still unclear.

Purpose

We assessed whether longer duration of cooling could provides a better neurological outcome in comatose survivors of out-of-hospital cardiac arrest treated with MTH.

Method 1

We conducted a multicenter retrospective study at 12 institutions to evaluate the efficacy of MTH in comatose survivors of out-of-hospital cardiac arrest treated with MTH between 2005 and 2009 in Japan (J-PULSE-Hypo). Selection of duration and procedure of cooling was determined individually by each institution. A cohort of 281 patients was registered during this study period and duration of cooling was recorded for a total of 251 enrolled patients. Patients were divided into 2 groups according to duration of cooling, namely, duration of cooling less than 36 hours in Group-A and more than or equal to 36 hours in Group-B.



Method 2

We assessed 30-day survival, favourable neurological outcome and complications.

A favourable neurological outcome was defined as a cerebral Pittsburgh performance category of 1 or 2 at day 30.

Complications were defined as blood transfusion, disseminated intravascular coagulation (DIC), lethal arrhythmia, infection and others.

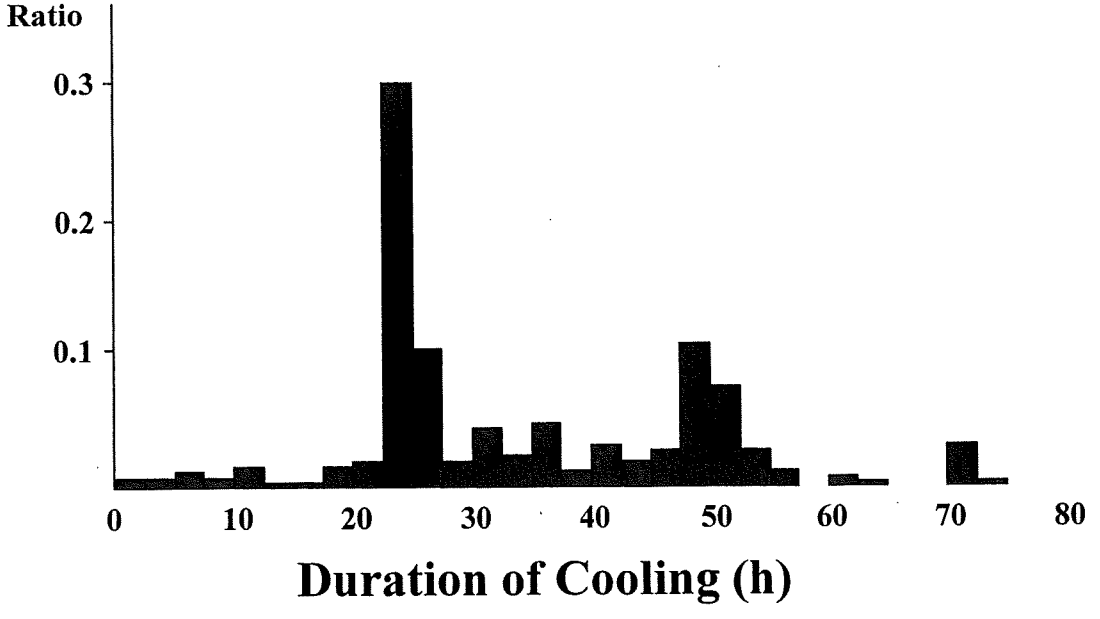
Statistical Analysis 1

Estimates for continuous variables are presented as medians (with interquartile ranges) and categorical variables as frequency counts and percentages. Differences in baseline characteristics were compared using the Mann–Whitney U-test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

Statistical Analysis 2

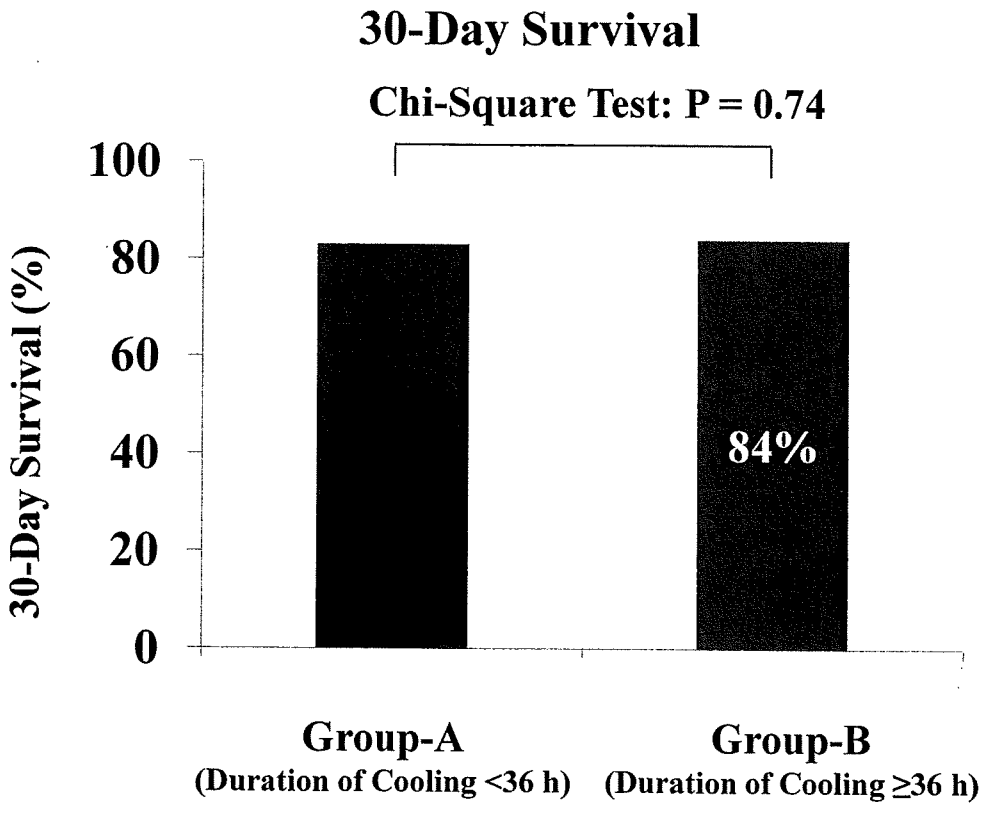
We used logistic regression to examine the association between duration of cooling for more than 36 hours and a favourable neurological outcome in (1) an unadjusted model, (2) a model adjusted for age and gender, and (3) a model adjusted for age, gender, witnessed cardiac arrest, by-stander CPR, initial rhythm and time interval from collapse to return of spontaneous circulation (ROSC). All tests were two-sided, and a P value of less than 0.05 was considered statistically significant.

Distribution of Duration of Cooling

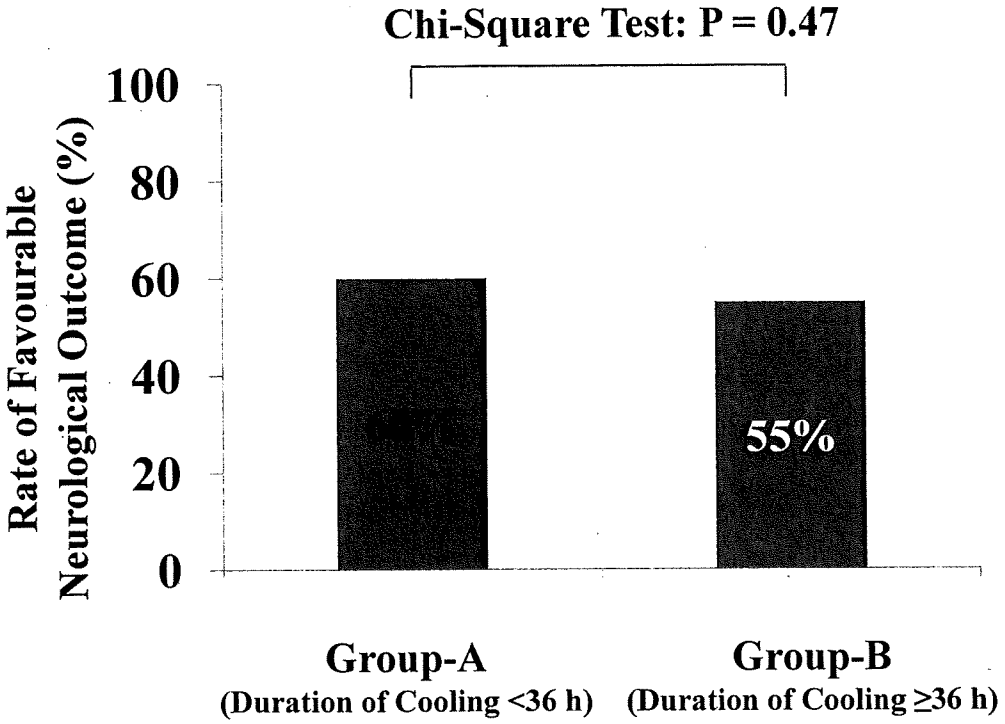


Baseline Characteristics of Study Patients

	Group-A (N = 150)	Group-B (N = 101)	P value
Age	61 (51 - 69)	58 (50 - 66)	0.16
Men	127 (85%)	84 (83%)	0.75
Witnessed Cardiac Arrest	136 (91)	84 (83%)	0.08
By-Stander CPR	76 (51%)	51 (51%)	0.98
Initial Rhythm			0.89
VF / Pulseless VT	107 (71%)	71 (71%)	
PEA	15 (10%)	7 (7%)	
Asystole	10 (7%)	7 (7%)	
Collapse to ROSC (min)	18 (11 – 30)	22 (13 – 37)	0.04
Total Epinephrine Dose (mg)	2 (2 – 3)	2 (2 – 4)	0.44
Emergency Coronary Angiography	61 (41%)	48 (48%)	0.28
Reperfusion Therapy	36 (24%)	28 (28%)	0.51



Favourable Neurological Outcome at 30-Day



Complications

	Group-A (N = 150)	Group-B (N = 101)	P Value
Any Complications	29 (19%)	41 (41%)	<0.001
Blood Transfusion	15 (10%)	16 (16%)	0.17
DIC	4 (3%)	4 (4%)	0.72
Lethal Arrhythmia	7 (5%)	10 (10%)	0.11
Infection	14 (9%)	27 (27%)	<0.001
Others	5 (3%)	5 (5%)	0.53

Odds Ratio of Duration of Cooling for Favourable Neurological Outcome

	Odds Ratio	95% CI	P Value
Unadjusted Model	0.83	0.50 - 1.38	0.47
Adjusted with Age, Gender	0.76	0.45 - 1.29	0.32
Adjusted with Covariates*	0.85	0.48 – 1.51	0.57

* Adjusted with age, gender, witnessed cardiac arrest, by-stander CPR, initial rhythm, time interval from collapse to ROSC

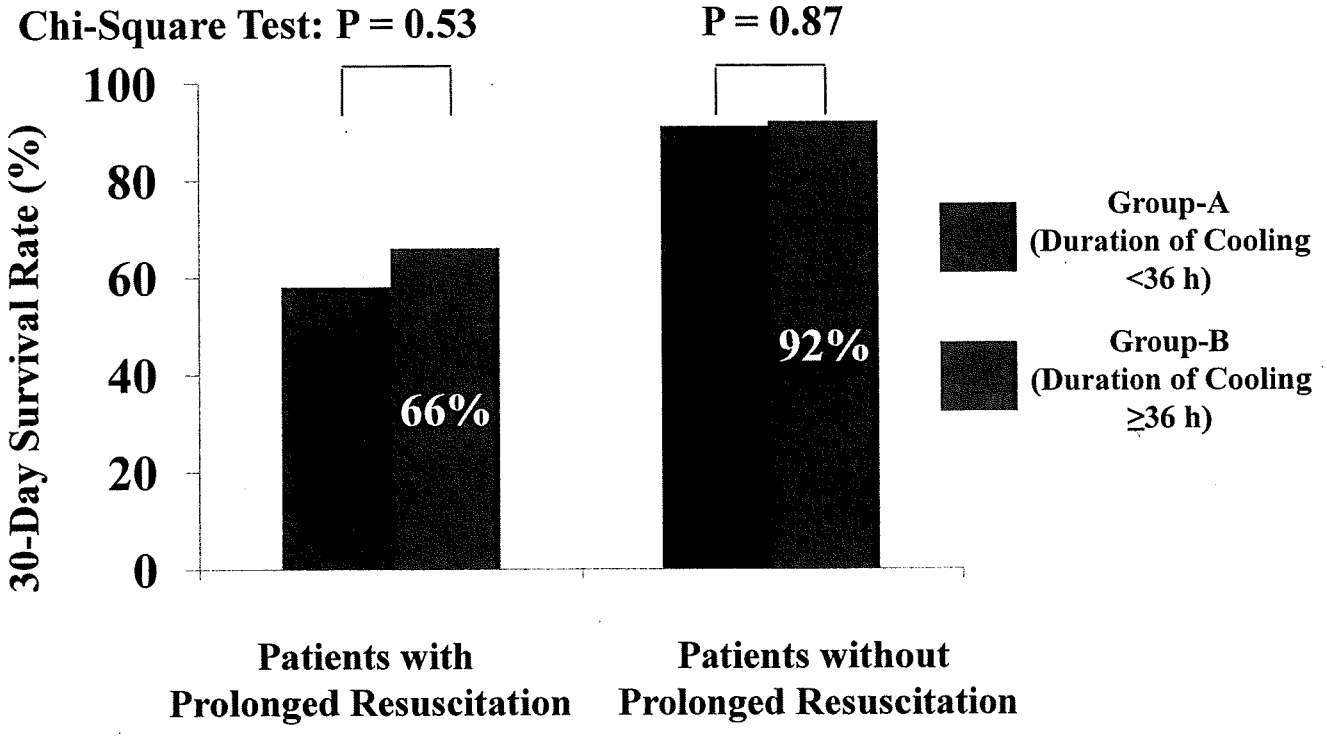
Subgroup Analysis

Because baseline severity of patients (time interval from collapse to ROSC) was different between the 2 groups, we provide additional analysis with prolonged resuscitation (time interval from collapse to ROSC of more than 30 min).

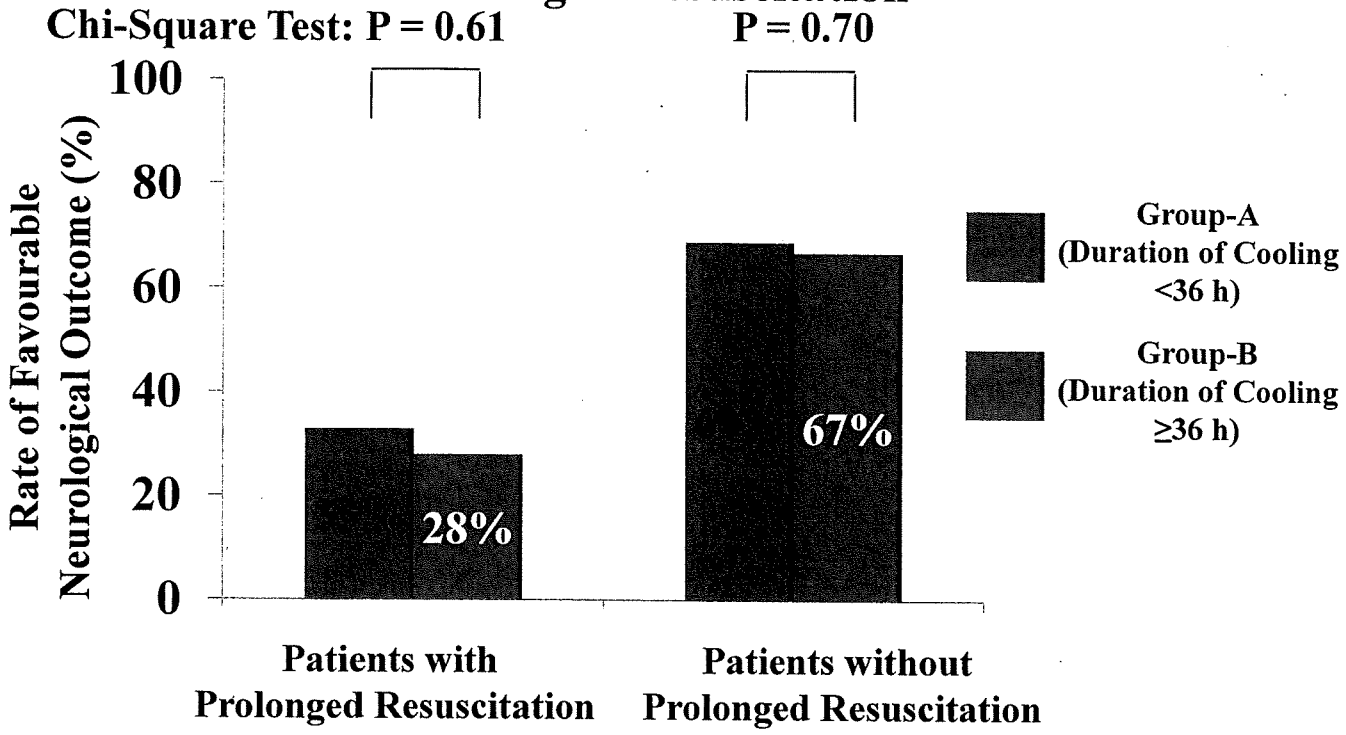
Baseline Characteristics of Patients with Prolonged Resuscitation

	Group-A (N = 39)	Group-B (N = 29)	P Value
Age	58 (53 - 67)	56 (50 - 63)	0.21
Men	37 (95%)	23 (79%)	0.06
Witnessed Cardiac Arrest	33 (85%)	18 (62%)	0.03
By-Stander CPR	22 (56%)	13 (45%)	0.34
Initial Rhythm			0.90
VF / Pulseless VT	27 (69%)	21 (75%)	
PEA	5 (13%)	2 (7%)	
Asystole	4 (10%)	3 (11%)	
Collapse to ROSC (min)	51 (36 – 68)	47 (40 – 75)	0.47
Total Epinephrine Dose (mg)	3 (2 – 4.5)	2 (2 – 5)	0.84
Emergency Coronary Angiography	22 (56%)	13 (45%)	0.34
Reperfusion Therapy	16 (41%)	9 (31%)	0.40

30-Day Survival of Patient with Prolonged Resuscitation



Favourable Neurological Outcome for Patient with Prolonged Resuscitation



Complications in Patients with Prolonged Resuscitation

	Group-A (N = 39)	Group-B (N = 29)	P value
Any Complications	14 (36%)	15 (56%)	0.11
Blood Transfusion	8 (21%)	7 (24%)	0.72
DIC	2 (5%)	2 (7%)	>0.99
Lethal Arrhythmia	4(10%)	4 (14%)	0.72
Infection	4 (10%)	9 (31%)	0.03
Others	2 (5%)	1 (3%)	>0.99

Summary

- ✓ In the entire cohort, there was no significant difference in the 30-day survival rate (83% vs. 84%, P = 0.74) and favourable neurological outcome (60% vs. 55%, P = 0.47) between the 2 groups. Complications occurred more frequently in group-B than in group-A (19% vs. 41%, P <0.01).
- ✓ Time interval from collapse to ROSC was significantly longer in group-A than in group-B(median 18 min vs. 22 min, P = 0.04).
- ✓ When adjusting for covariates, no significant association was observed between cooling duration of more than 36 hours and favourable neurological outcome.
- ✓ In patients with prolonged resuscitation, similar findings were observed.

Study Limitations

This study was a non-randomized study and has limitations common to all retrospective investigations. The duration of cooling was not analyzed according to an intention-to-treat policy in this study. As more critically ill patients could have cooled longer, we attempted to adjust for possible selection bias by multivariate and subgroup analysis.

Conclusions

Duration of Cooling of more than 36 hours may not provide better neurological outcome, but increase complications in comatose survivors of out-of-hospital cardiac arrest treated with MTH.

National Cardiovascular Center

Impacts of Percutaneous Assisted Devices and Mild Hypothermia Therapy for Out-of-Hospital Cardiac Arrest in Patients from Multicenter Hypothermia Registry in Japan: J-Pulse-Hypo registry

Nobuaki Kokubu
Hiroyuki Yokoyama, Yoritaka Otsuka,
Nobihito Yagi, Futoshi Yamanaka, Naohiro Yonemoto*,
Ken Nagao[§], Hiroshi Nonogi
National Cardiovascular Center, Suita, Japan
*Kyoto University, Kyoto, Japan
[§]Nihon University, Tokyo, Japan

National Cardiovascular Center

Presenter Disclosure Information

Nobuaki Kokubu, MD
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