

**Impact of Target Core Temperature on  
Neurological Outcome of Cardiac Arrest Patients  
Treated with Therapeutic Hypothermia**

**Shunji Kasaoka**, Ryosuke Tsuruta, Yamaguchi Univ Hosp, Ube, Japan; Ken Nagao, Nihon Univ, Tokyo, Japan; Naohiro Yonemoto, Natl Ctr of Neurology and Psychiatry, Tokyo, Japan; Hiroyuki Yokoyama, Hiroshi Nonogi, Natl Cerebral and Cardiovascular Ctr, Osaka, Japan; the J-PULSE-Hypo Investigators



**Background**

Therapeutic hypothermia improves neurological outcome in patients with out-of-hospital cardiac arrest. However, optimal target core temperature remains unclear.

**Objective**

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

**Methods**

We conducted a multi-center registry at 14 institutions to evaluate the effect of therapeutic hypothermia in out-of-hospital cardiac arrest patients between January 2005 and December 2009. 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 2009 at each hospital.

**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 poor daily activity.

**Methods (cont'd)**

**Analysis**

- Patients were divided into the L group (32~33°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 452 patients were enrolled. Two patients were excluded because target temperature was unknown. The median interval from collapse to return of spontaneous circulation was 25 minutes.
2. Between the L group (n=43) and the M group (n=407), the rates of survivors (77% vs. 77%) and favorable outcomes (60% vs. 55%) were not statistically different.

## Results (cont'd)

3. As compared with the M group, the L group had significantly longer cooling time (36 hrs vs. 25 hrs, p=0.0021) and lower rate of core cooling method (28% vs. 50%, p=0.0056).
4. The L group had significantly higher rates of inadequately controlled core temperature (49% vs. 29%, p=0.0073), and side effects of hypothermia (48% vs. 29%, p=0.0014).
5. Of the side effects, the rate of arrhythmia was significantly different (19% vs. 5%, p=0.0004).

**Table 1. Baseline Characteristics**

Number of patients	450
Age (years)	60 (52-68)
Male (%)	371 (82%)
Witnessed cardiac arrest (%)	390 (87%)
Performed bystander CPR (%)	230 (51%)
Time from collapse to ROSC (min)	25 (17-40)
Initial arrest rhythm: VF/VT (%)	353 (78%)

**Table 2. Method of Hypothermia**

<b>Cooling methods</b>	
- Surface cooling (%)	227 (50%)
- Core cooling (%)	217 (48%)
- Infusion of ice-cold fluid (%)	239 (53%)
<b>Duration of cooling (hours)</b>	25 (24-43)
<b>Target core temperature (°C)</b>	
- 32.0 ~ 33.9°C	43 (10%)
- 34.0 ~ 35.0°C	407 (90%)

**Table 3. Comparison of Outcome**

	L group	M group	p Value
Number of patients	43	407	
Age (years)	52 (41-61)	61 (53-69)	0.0001
Target temperature (°C)	33 (33-33)	34 (34-34)	<0.0001
Duration of cooling (hrs)	36 (24-50)	25 (24-40)	0.0021
Core cooling (%)	31 (72%)	203 (50%)	0.0056
Survival (%)	33 (77%)	315 (77%)	0.9227
Favorable outcome (%)	26 (60%)	223 (55%)	0.4766

**Table 4. Side Effects of Hypothermia**

	L group	M group	p Value
Inadequately controlled core temperature (%)	21 (49%)	114 (29%)	0.0073
Over-cooling (%)	15 (35%)	79 (20%)	0.0228
Side effects (%)	20 (48%)	118 (29%)	0.0140
- Arrhythmia	8 (19%)	20 (5%)	0.0003
- Infection	4 (10%)	59 (15%)	0.3683
- Blood transfusion	8 (19%)	55 (14%)	0.3359

**Table 4 (cont'd)**  
**Side Effects of Hypothermia**

**Definition**

- 1) Inadequately controlled core temperature:  
 Core temperature exceeds target temperature  $\pm 0.5$  °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 in cardiac arrest patients.
2. The lower target core temperature may cause increase of side effects.
3. To control core temperature adequately, further studies of cooling methods and managements are needed.

**Study Organization**

**Principle investigator:**  
 Hiroshi Nonogi

**Working members:**

Ken Nagao, Hiroyuki Yokoyama Yoshio Tahara,  
 Shinichi Shirai, Shunji Kasaoka, Kazunori Kashiwase,  
 Yuichi Motomura, Tomotaka Sawano, Mamoru Hase,  
 Yuji Yasuga, Nobuaki Kokubu, Naoyuki Ohtani  
 Hideaki Arimoto, Yasuhiro Kuroda, Hiroshi Hazui

**Biostatisticians:**

Naohiro Yonemoto, Akiko Kada

**Participating institutions:**

National Cerebral and Cardiovascular Center	Sapporo Medical University Hospital
Nihon University Surugadai Hospital	Yokohama City University Medical Center
Osaka Police Hospital	Kokura Memorial Hospital
Saga University Hospital	Saiseikai Senni Hospital
Hiroshima City Hospital	Osaka City General Hospital
<u>Yamaguchi University Hospital</u>	Miehima Emergency Critical Center
Kagawa University Hospital	Sumitomo Hospital



**For information regarding this presentation:**

Shunji Kasaoka, MD  
 AMEC<sup>3</sup>, Yamaguchi University Hospital  
 1-1-1 Minami-Kogushi, Ube 755-8505, Japan  
 E-mail: skasa@yamaguchi-u.ac.jp

**The Relationship Between Time Interval from Collapse to  
Return of Spontaneous Circulation and Neurologically Intact  
Survival for Patients Treated with Hypothermia after  
Non-Ventricular Fibrillation Arrest Out of Hospital.**

**BACKGROUND**

Clinical evidence strongly supports mild therapeutic hypothermia for unconscious patients with out-of-hospital cardiac arrest due to ventricular fibrillation (VF), but there are insufficient data that hypothermia had neurological benefit for those with non-VF arrest.

**METHODS**

We did a multicenter observational study of therapeutic hypothermia for unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest. The J-PULSE Hypothermia committee entrusted each hospital with timing of cooling, cooling methods, target temperature, duration, and rewarming rate. The primary endpoint was a favorable neurological outcome at hospital discharge.

**RESULTS**

Of the 452 unconscious adult patients treated with therapeutic

hypothermia, 435 who were cooled to 32 °C to 34 °C were included; 94 were non-VF arrest (non-VF group) and 341 were VF arrest (VF group). The non-VF group had a lower frequency of favorable neurological outcome than the VF group (27.7% vs. 63.7%,  $p < 0.0001$ ). However, in the subgroups of patients who were divided into quartiles on the basis of collapse-to-ROSC interval, the non-VF group had a similar frequency of favorable neurological outcome than the VF group among patients with the quartile-1 interval (92 % vs. 89 %,  $p = 0.75$ ). The non-VF group had lower frequencies of favorable neurological outcome than the VF group among patients with each quartile-2, quartile-3 and quartile-4 interval. In a multiple logistic-regression analysis among patients with the interval of quartile-1, non-VF arrest was not an independent predictor of a favorable neurological outcome with adjusted odds ratios of 0.53 (95% CI, 0.06-4.70,  $p = 0.56$ ). The area under the ROC curve in the non-VF group was 0.82, and a cut off value of the collapse-to-ROSC interval for identification of a favorable neurological outcome was 25 minutes. A frequency of favorable neurological outcome was 58 % in non-VF patients who achieved ROSC within 25 minutes after cardiac arrest.

## CONCLUSION

Therapeutic hypothermia for non-VF patients has neurological benefits

when the ROSC was achieved within 25 minutes after cardiac arrest.

318

# The Relationship Between Time Interval from Collapse to Return of Spontaneous Circulation and Neurologically Intact Survival for Patients Treated with Hypothermia after Non-Ventricular Fibrillation Arrest Out of Hospital.

**Taketomo Soga, Ken Nagao, Hiroyuki Yokoyama, Naohiro Yonemoto, Hiroshi Nonogi and J-PULSE-Hypo investigators**

## Introduction

In recent years, unconscious patients treated with mild therapeutic hypothermia after out-of-hospital cardiac arrest has been reported to have an improved neurological outcome. In 2002, two randomized studies of mild therapeutic hypothermia after out-of-hospital cardiac arrest showed a neurological benefit with a low risk of complications. In 2003, the International Liaison Committee on Resuscitation (ILCOR) recommended that unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32–34°C for 12–24 hours when the initial rhythm was ventricular fibrillation (VF), and such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest. Clinical evidence strongly supported mild hypothermia as an effective therapy for patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest, but the patients who may benefit from this treatment have not been fully elucidated.

The optimal candidates, temperature, the timing of initiation, the cooling duration and the rate for rewarming have not been defined clinically and should be established.

In Japan, there are several reports on mild therapeutic hypothermia for unconscious patients after out-of-hospital cardiac arrest, but these are almost single-center trial.

## Study Organization

**Principle Investigator:**  
Hiroshi Nonogi

**Working members:**

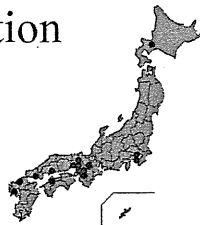
Ken Nagao, Hiroyuki Yokoyama, Yoshio Tahara, Shinichi Shirai, Shunji Kasaoka, Kazunori Kashiwase, Yuichi Motomura, Tomotaka Sawano, Mamoru Hase, Yuji Yasuga, Nobuaki Kokubu, Naoyuki Ohtani, Hideaki Arimoto, Yasuhiro Kuroda, Hiroshi Hazui

**Biostatisticians:**

Naohiro Yonemoto, Akiko Kada

**Participating Institution:**

National Cerebral and Cardiovascular Center Sapporo Medical University Hospital  
Nihon University Surugadai Hospital Yokohama City University Medical Center  
Osaka Police Hospital Kokura Memorial Hospital  
Saga University Hospital Saiseikai Senri Hospital  
Hiroshima City Hospital Osaka City General Hospital  
Yamaguchi University Hospital Mishima Emergency critical Center  
Kagawa University Hospital Sumitomo Hospital



AHA Res 2010

## Abstract

### BACKGROUND

Clinical evidence strongly supports mild therapeutic hypothermia for unconscious patients with out-of-hospital cardiac arrest due to ventricular fibrillation (VF), but there are insufficient data that hypothermia had neurological benefit for those with non-VF arrest.

### METHODS

We did a multicenter observational study of therapeutic hypothermia for unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest. The J-PULSE Hypothermia committee entrusted each hospital with timing of cooling, cooling methods, target temperature, duration, and rewarming rate. The primary endpoint was a favorable neurological outcome at hospital discharge.

### RESULTS

Of the 452 unconscious adult patients treated with therapeutic hypothermia, 435 who were cooled to 32 °C to 34 °C were included, 94 were non-VF arrest (non-VF group) and 341 were VF arrest (VF group). The non-VF group had a lower frequency of favorable neurological outcome than the VF group (27.7% vs. 63.7%,  $p < 0.0001$ ). However, in the subgroups of patients who were divided into quartiles on the basis of collapse-to-ROSC interval, the non-VF group had a similar frequency of favorable neurological outcome than the VF group among patients with the quartile-1 interval (92% vs. 89%,  $p = 0.75$ ). The non-VF group had lower frequencies of favorable neurological outcome than the VF group among patients with each quartile-2, quartile-3 and quartile-4 interval. In a multiple logistic-regression analysis among patients with the interval of quartile-1, non-VF arrest was not an independent predictor of a favorable neurological outcome with adjusted odds ratios of 0.53 (95% CI, 0.06–4.70,  $p = 0.56$ ). The area under the ROC curve in the non-VF group was 0.82, and a cut off value of the collapse-to-ROSC interval for identification of a favorable neurological outcome was 25 minutes. A frequency of favorable neurological outcome was 58% in non-VF patients who achieved ROSC within 25 minutes after cardiac arrest.

### CONCLUSION

Therapeutic hypothermia for non-VF patients has neurological benefits when the ROSC was achieved within 25 minutes after cardiac arrest.

## ClinicalTrials.gov

A Service of the U.S. National Institutes of Health

### Multicenter Registry Study With Therapeutic Hypothermia After Cardiac Arrest in Japan (J-PULSE-HYPO)

This study is currently recruiting participants.  
Verified by National Cardiovascular Center, Japan, May 2009

#### Study Population

Patients with therapeutic hypothermia after cardiac arrest from 2005 to 2009 in each hospitals.

#### Criteria

##### Inclusion Criteria:

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

##### Exclusion Criteria:

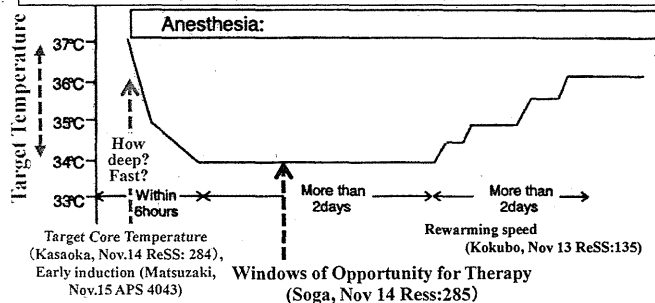
- Patients with:
  - pregnancy
  - acute aortic dissection
  - pulmonary thromboembolism
  - drug poisoning
  - poor daily activity

J-PULSE  
hypothermia  
registry

## 10 Clinical Questions from J-PULSE-Hypo in 2010

### Patients characteristic

Initial Patients Evaluation (blood exam.) (Toh, Nov 13 ReSS:133, Kasai, Nov 14 ReSS:275, Kashiwase, Nov 14 ReSS:282, Shirai, Nov 15 APS 4048), Non-VF (Tahara, Nov 13 ReSS: 137), PCPS with Hemodynamic Compromised State (Kokubu, Nov 14 ReSS:262)



# Hypothermia Protocol

After sedation with analgesia and in some cases, cold intravenous fluid (4°C) was administered over 30-60 min to initiate hypothermia.

- The methods of initiation or maintenance of hypothermia was attempted by one of the following four devices or two methods;
  - 1) Surface cooling (a: Cooling Blanket (Blanketrol II, CSZ medical, Cincinnati, OH, USA, b: Cooling device with self-adhesive, hydrogel-coated pads (Arctic Sun, Medivance, Louisville, KY, USA),
  - 2) Blood cooling (c: Extracorporeal direct blood cooling (KTEK-III, Kawasumi, Tokyo, Japan, d: Endovascular cooling device (CoolGard 3000, Alsius, Irvine, CA, USA).
- Mild hypothermia (32-34°C) was maintained for 24-72 hours.
- Re-warming was conducted slowly and gradually and took at least 24-72 hours.
- ★ Protocol of hypothermia was determined in each institutional state.

# Study endpoints

The primary endpoint of this study was a favorable neurological outcome at 30 days, 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 (vegetative state), and 5 (death). The secondary endpoint was survival to hospital discharge (Glasgow-Pittsburgh cerebral performance category of 1, 2, 3, or 4) or death at 24 hours, 7 days, 30 days.

# Purpose

We investigated the relationship between time interval from collapse to ROSC and neurologically intact survival for patients treated with hypothermia after non-VF arrest out of hospital.

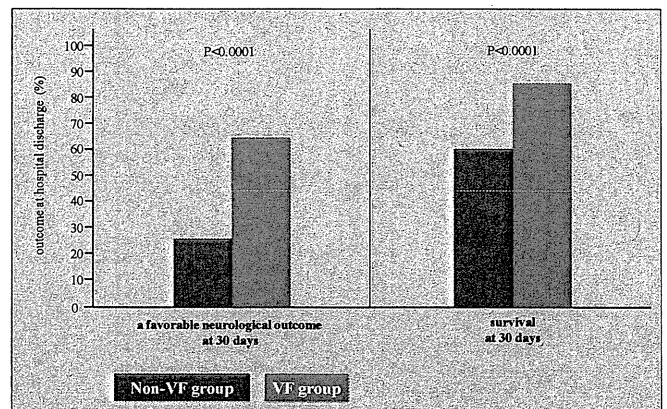
Baseline characteristics of patients according to the initial cardiac arrest rhythm

	Non-VF group n=94	VF group n=341	P value
Age, yr	63 (52-71)	60 (52-68)	0.0626
Male	76 (81%)	285 (84%)	0.5333
Cause of cardiac arrest*			0.0916
Acute coronary syndrome	43 (78%)	218 (76%)	
Cardiomyopathy	3 (5%)	23 (8%)	
Arrhythmia	4 (7%)	37 (13%)	
Others	5 (9%)	8 (3%)	
Bystander CPR	51 (54%)	171 (50%)	0.4805
Time interval (min)			
From collapse to call receipt	0 (0-0)	0 (0-0)	0.4169
From call receipt to patient's side	6 (4-8)	5 (4-7)	0.3297
From patient's side to arrival at emergency room	12 (6-19)	15 (10-22)	0.0243
From collapse to ROSC	31 (21-45)	24 (16-40)	0.0127
From collapse to attainment of target temperature	278 (175-482)	294 (157-449)	0.5285

Baseline characteristics of patients according to the initial cardiac arrest rhythm

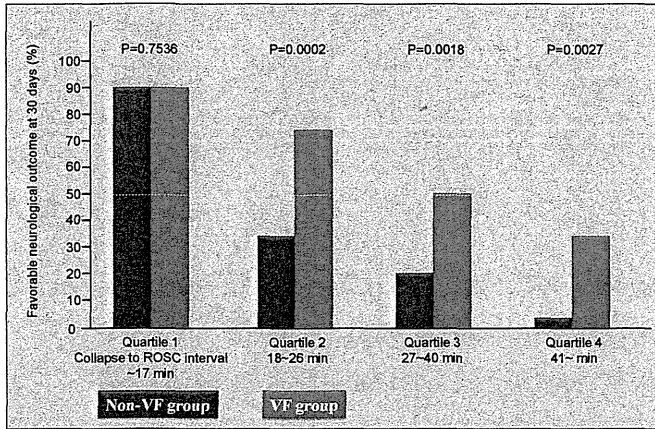
	Non-VF group n=94	VF group n=341	P value
Cooling duration*			0.8593
24 hours	40 (47%)	145 (47%)	
48 hours	34 (40%)	115 (38%)	
72 hours	11 (13%)	46 (15%)	
Cooling methods*			0.3328
surface cooling	50 (54%)	161 (49%)	
extracorporeal cooling	42 (46%)	170 (51%)	
Systolic blood pressure at start hypothermia (mmHg)	120 (97-150)	128 (107-153)	0.0872
Heart rate at start hypothermia (/min)	51 (54%)	171 (50%)	0.4805
Coronary angiography for ACS	39/43 (91%)	213/218 (98%)	0.0009
Coronary reperfusion for ACS	22/43 (51%)	166/218 (76%)	0.0009
TIMI flow grade 3 after reperfusion	17/22 (77%)	152/163 (93%)	0.0123

Favorable neurological outcome at 30 days (primary end points) and survival at hospital discharge (secondary end points) for patients





Association between the quartiles of the collapse-to-ROSC interval and the frequencies of favorable neurological outcome at 30 days

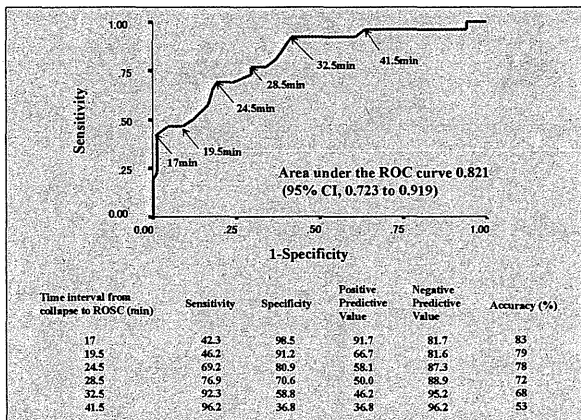


Adjusted odds ratios for a favorable neurological outcome at 30 days survival associated with selected factors

in the quartile 1			
Variable	Odds ratio	Confidence interval	p value
Age	0.941	0.887-0.999	0.0477
Male	1.792	0.415-7.740	0.4342
Bystander CPR attempt	1.125	0.326-3.881	0.8517
VF/VT at initial rhythm	0.525	0.059-4.704	0.5648

in the quartile 2,3,4			
Variable	Odds ratio	Confidence interval	p value
Age	0.960	0.942-0.979	<0.0001
Male	0.967	0.494-1.892	0.9222
Bystander CPR attempt	1.539	0.946-2.503	0.0824
VF/VT at initial rhythm	5.484	2.896-10.386	<0.0001

Receiver-operating-characteristics (ROC) curves in the non-VF group for various cutoff levels of the collapse-to-ROSC interval to differentiate a favorable neurological outcome and an unfavorable neurological outcome at 30 days survival



Outcome by duration of cardiac arrest in the non-VF group

	Time interval from collapse to ROSC		
	<25 min	≥25 min	p value
Favorable neurological outcome	58.1%	12.7%	<0.0001

## Discussion

This is the first multicenter study for therapeutic hypothermia in Japan. Recently our government has made an investigation of victims with out-of-hospital cardiac arrest according to the Utstein Style reporting guidelines. Each year 110,000 people have developed cardiac arrest outside the hospital, of those, 6% had a favorable neurological outcome. Our results showed that 55.8% of patients in who received hypothermia after ROSC following out-of-hospital cardiac arrest had a favorable neurological outcome at 30 days.

Compared non-VF group with VF group, there was significant difference in the favorable neurological outcome (p<0.0001). However, in the subgroups of patients who were divided into quartiles on the basis of collapse-to-ROSC interval, the non-VF group had a similar frequency of favorable neurological outcome than the VF group among patients with the quartile-1 interval (92% vs. 89%, p=0.75). A cut off value of the collapse-to-ROSC interval for identification of a favorable neurological outcome was 25 minutes. A frequency of favorable neurological outcome was 58% in non-VF patients who achieved ROSC within 25 minutes after cardiac arrest.

The brain damage in patients with cardiopulmonary arrest is caused by global cerebral ischemia following the stop of systemic and brain circulation. Therapeutic hypothermia for non-VF patients would have neurological benefits when the ROSC was achieved within shorter collapse-to-ROSC interval after cardiac arrest.

## Conclusions

Therapeutic hypothermia for non-VF patients has neurological benefits when the ROSC was achieved within 25 minutes after cardiac arrest.

## Impact of Hyperglycemia at Admission on Thirty Days Clinical Outcomes for the Out-of-hospital Cardiac Arrest of Patients Acute Coronary Syndrome Undergoing Coronary Intervention with Hypothermia Therapy.

**Background:** Hyperglycemia affected the clinical result of acute myocardial infarction underwent coronary intervention. The aim of this study was to evaluate the effect of hyperglycemia at admission on the 30-days clinical outcomes of the patients (pts) with cardiac arrest due to acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with mild therapeutic hypothermia (MHT).

**Methods:** Data over a five-year period (2005-2009) were obtained for 452 patients treated with MHT from a multicenter registry in Japan. Of these patients, all of 193 pts were diagnosed with ACS by emergency angiography immediately after recovery of spontaneous circulation (ROSC), and were subsequently treated with MHT and PCI. These patients were divided into groups based on the blood glucose (BS) at admission; Group A: BS at admission >300mg/dl and Group B: BS at admission ≤300mg/dl. Cerebral performance category (CPC) with levels 1 (Normal mental performance), 2 (moderate disability), 3 (severe disability), 4 (vegetative state), 5 (death) was used at 30days. Poor neurologic outcome was defined in CPC 3, 4 and 5.

**Results:** Patient demographics of Group A (n=71) were younger (mean age 58 vs. 64,  $p<0.0001$ ), longer time from arrest to ROSC (42min. vs. 30 min.,  $p=0.0018$ ). The proportions of shockable rhythm and the time to achieve target temperature were not different. There was no significantly different in survival rate (74.1% vs. 79.1%,  $p=0.4775$ ) between the two groups, however, neurologic outcome was significantly better in group B compared with group A (35.2% vs. 60.0%,  $p=0.0010$ ). Logistic regression analysis revealed that the predictors of poor neurologic outcome were shockable rhythm (Odds ratio [OR]: 12.0,  $p<0.0001$ ), age over 70 (OR: 7.7,  $p<0.0001$ ), time from collapse to ROSC (OR 4.3,  $p<0.0001$ ), and BS at admission over 300mg/dl (OR: 2.8,  $p=0.0060$ ).

**Conclusions:** Hyperglycemia at admission did not affect the mortality; however, had an impact on neurologic outcome for the patients with ROSC after cardiac arrest due to ACS undergoing PCI with MHT.

## Background

AHA 2010  
Impact of Hyperglycemia at Admission on Thirty Days Clinical Outcomes for the Out-of-hospital Cardiac Arrest of Patients Acute Coronary Syndrome Undergoing Coronary Intervention with Hypothermia Therapy.

Hyperglycemia affected the clinical result of acute myocardial infarction underwent coronary intervention. Furthermore, hyperglycemia also had an impact on neurologic outcome in the case of post resuscitation state. The aim of this study was to evaluate the effect of hyperglycemia at admission on the 30-days clinical outcomes of the patients (pts) with cardiac arrest due to acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) with mild therapeutic hypothermia (MHT).

## Methods

Data over a five-year period (2005-2009) were obtained for 452 patients treated with MHT from a multicenter registry in Japan. Of these patients, all of 193 pts were diagnosed with ACS by emergency angiography immediately after recovery of spontaneous circulation (ROSC), and were subsequently treated with MHT and PCI.

Cerebral performance category (CPC) with levels 1 (Normal mental performance), 2 (moderate disability), 3 (severe disability), 4 (vegetative state), 5 (death) was used at 30days. Poor neurologic outcome was defined in CPC 3, 4 and 5.

## Study Organization

### Principle Investigator:

Hiroshi Nonogi

### Working members:

Ken Nagao, Hiroyuki Yokoyama Yoshio Tahara, Shinichi Shirai, Shunji Kasaoka, Kazunori Kashiwase, Yuichi Motomura, Tomotaka Sawano, Mamoru Hase, Yuji Yasuga, Nobuaki Kokubu, Naoyuki Ohtani, Hideaki Arimoto, Yasuhiro Kuroda, Hiroshi Hazui

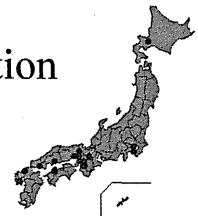
### Biostatisticians:

Naohiro Yonemoto, Akiko Kada

### Participating institution:

National Cerebral and Cardiovascular Center  
Nihon University Surugadai Hospital  
Osaka Police Hospital  
Saga University Hospital  
Hiroshima City Hospital  
Yamaguchi University Hospital  
Kagawa University Hospital

Sapporo Medical University Hospital  
Yokohama City University Medical Center  
Kokura Memorial Hospital  
Saiseikai Senri Hospital  
Osaka City General Hospital  
Mishima Emergency critical Center  
Sumitomo Hospital

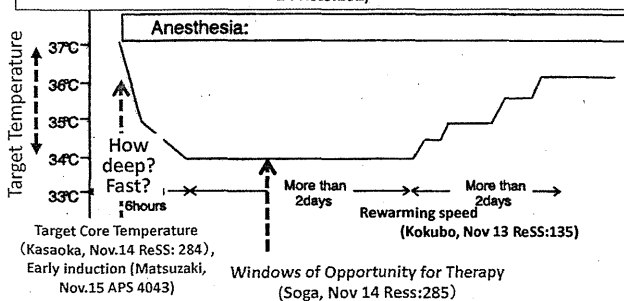


AHA Res 2010

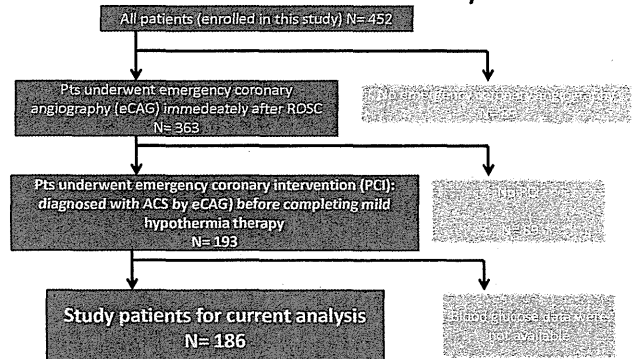
## 10 Clinical Questions from J-PULSE-Hypo in 2010

### Patients characteristic

Initial Patients Evaluation (blood exam.) (Toh, Nov 13 ReSS:133, Kasai, Nov 14 ReSS:275, Kashiwase, Nov 14 ReSS:282, Shirai, Nov 15 APS 4048), Non-VF (Tahara, Nov 13 ReSS: 137), PCPS with Hemodynamic Compromised State (Kokubu, Nov 14 ReSS:262)

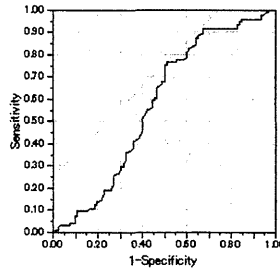


## Patients for current analysis

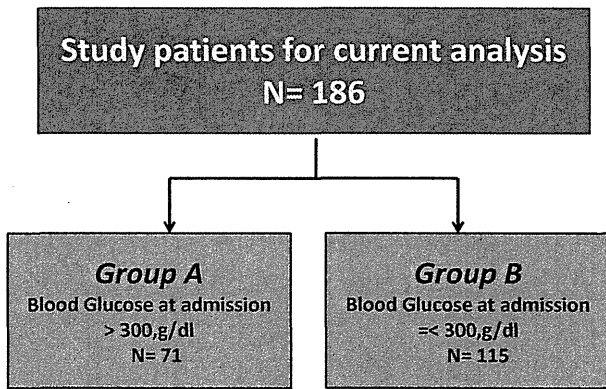


ROSC: Recovery of spontaneous circulation, ACS: Acute coronary syndrome

These patients were divided into groups based on the blood glucose (BS) at admission; Group A: BS at admission >300mg/dl and Group B: BS at admission =<300mg/dl.



Blood sugar	1-Specificity	Sensitivity
272.0000	0.4674	0.6064
274.0000	0.4674	0.6170
276.0000	0.4674	0.6277
284.0000	0.4674	0.6383
287.0000	0.4674	0.6489
289.0000	0.4782	0.6596
290.0000	0.4891	0.6702
293.0000	0.4891	0.6809
294.0000	0.5000	0.6909
295.0000	0.5000	0.6915
296.0000	0.5000	0.7021
299.0000	0.5000	0.7224
300.0000	0.5000	0.7240
301.0000	0.5000	0.7447
306.0000	0.5000	0.7653
307.0000	0.5109	0.7653
308.0000	0.5109	0.7660
309.0000	0.5117	0.7660
311.0000	0.5326	0.7660
312.0000	0.5435	0.7660
313.0000	0.5543	0.7660
315.0000	0.5543	0.7766
316.0000	0.5761	0.7766
323.0000	0.5670	0.7766
328.0000	0.5978	0.7872
329.0000	0.5978	0.7978



### Baseline Patient Characteristics

	Group A (BS>300mg/dl)	Group B(BS=<300mg/dl)	P
Age	57	64	<0.0001
Man (%)	84.5	90.4	0.2239
Age>70 (%)	14.1	26.1	0.0529
Bystander CPR (%)	46.1	59.2	0.833
Shokable Rhythm (%)	78.6	87.6	0.1037
Hypertension (%)	35.2	30.4	0.4984
Diabetes (%)	22.5	10.4	0.025
ROSC before Admission (%)	42.3	63.5	0.0047
Hemoglobin (g/dl)	13.4	13.8	0.226
Serum Pottasium (mEq/l)	4.04	3.92	0.3478
Cre >1.5 mg/dl (%)	5.6	17.4	0.0143
Blood sugar at admission (mg/dl)	396	226	<0.0001
Base Excess	-12.2	-15.7	0.0001

ROSC: Recovery of spontaneous circulation

### Hypothermia data

	Group A (BS>300mg/dl)	Group B(BS=<300mg/dl)	P
CA-CPR (min)	8.6	9.1	0.6347
CA-ROSC (min)	42.3	31.0	0.0018
CA-Target temperature (min)	352	371	0.6221
Blood coolong (%)	57.7	47.0	0.1527
Cooling duration (hours)	30.3	51.3	0.4315
MHT induction-target temperature (min)	242	238	0.9062

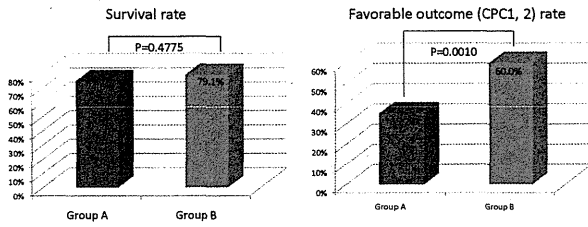
CA: Cardiac arrest, CPR: Cardiopulmonary resuscitation, MHT: mild hypothermia therapy

### Intervention data

	Group A (BS>300mg/dl)	Group B(BS=<300mg/dl)	P
Stent implantation (%)	91.3	91.2	0.9859
LMT culprit (%)	2.8	3.3	0.594
LAD culprit (%)	59.2	68.7	0.1849
IABP (%)	66.2	54.8	0.1239
PCPS (%)	42.3	25.2	0.0153

LMT: Left main trunk, LAD: left anterior descending artery, IABP: Intra-aortic balloon pumping, PCPS: Percutaneous cardiopulmonary support device

## Clinical outcomes @ 30days



Group A: Blood sugar at admission >300mg/dl  
 Group B: Blood sugar at admission <300mg/dl

## Predictors of poor neurologic outcomes @ 30 days

	Univariate			Multivariate		
	Odds ratio	95% C.I	p	Odds ratio	95% C.I	p
Age>70	4.06	1.90-9.33	0.0002	9.83	3.70-29.19	<0.0001
Shockable rhythm	0.08	0.02-0.25	<0.0001	0.115	0.02-0.39	0.0002
Base excess	0.93	0.88-0.98	0.005			
CA-ROSC	1.04	1.02-1.06	<0.0001	1.03	1.00-1.050	0.0254
CA-Target temperature	0.15	0.03-0.76	0.0212			
IABP	2.39	1.32-4.39	0.004			
PCPS	4.28	2.21-5.15	<0.0001			
BS>300mg/dl	2.76	1.51-5.15	0.001	2.58	1.16-5.89	0.0192

CA-ROSC: Time from collapse to ROSC, CA-Target temperature: Time from collapse to target Temperature, IABP: Intra-aortic balloon pumping, PCPS: Percutaneous cardiopulmonary support device

## Conclusions

Hyperglycemia at admission did not affect the mortality; however, had an impact on neurologic outcome for the patients with ROSC after cardiac arrest due to ACS undergoing PCI with MHT.

**Ammonia as a Biochemical Marker of Neurological Outcomes for  
Patients Treated with Therapeutic Hypothermia after  
Out-of-Hospital Cardiac Arrest**

The Japanese Pulse Hypothermia Study(J-PULSE Hypothermia) Group

Asuka Kasai, Ken Nagao,

**BACKGROUND**

Excessive accumulation of ammonia induces neuronal metabolic derangements, promotes astrocyte swelling, and perturbs cerebral nitric oxide metabolism. Although studies have shown there is a correlation between increase in blood ammonia level and hepatic encephalopathy, few data are available for patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest.

**METHODS**

We did a multicenter observational study of therapeutic hypothermia for

unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest. The J-PULSE Hypothermia committee entrusted each hospital with timing of cooling, cooling methods, target temperature, duration, rewarming rate and measurement of blood ammonia. The primary endpoint was a favorable neurological outcome at hospital discharge.

## RESULTS

Of the 432 unconscious adult patients who were treated with therapeutic hypothermia (32 °C to 34 °C) after ROSC, 143 whose blood ammonia level was measured on arrival at the emergency room were included in this study. A total of 82 (57.3%) of the 143 patients had a favorable neurological outcome, and the ammonia level was lower among such patients than among those who had an unfavorable neurological outcome (a median, 72  $\mu$  g/dl vs. 110  $\mu$  g/dl;  $p=0.0002$ ). Significant differences were seen in frequency of a favorable neurological outcome among the patients who were divided into quartiles of ammonia levels (71% in the Q-1, 67% in the Q-2, 67% in the Q-3, 25% in the Q-4;  $p<0.001$ ), and the subgroups of patients with VF and non-VF. A multiple logistic-regression analysis of a favorable neurological outcome after quartiles of ammonia levels showed that the adjusted odds ratios of the Q-4 was 0.26 (95% CI, 0.03-0.93,  $p=0.039$ ). In the

area under the ROC curve, the ammonia cutoff value of 93.5  $\mu$  g/dl had the highest combined sensitivity and specificity with an accuracy of 73% for the identification of favorable neurological outcome.

## CONCLUSION

The measurement of ammonia on ER arrival was found to provide valuable information regarding long-term neurologically intact survival in adult patients treated with therapeutic hypothermia.

(327)



## Abstract

### BACKGROUND

Excessive accumulation of ammonia induces neuronal metabolic derangements, promotes astrocyte swelling, and perturbs cerebral nitric oxide metabolism. Although studies have shown there is a correlation between increase in blood ammonia level and hepatic encephalopathy, few data are available for patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest.

### METHODS

We did a multicenter observational study of therapeutic hypothermia for unconscious adult patients with return of spontaneous circulation (ROSC) after out-of-hospital cardiac arrest. The J-PULSE Hypothermia committee enlisted each hospital with the timing of cooling, cooling methods, target temperature, duration, rewarming rate and measurement of blood ammonia. The primary endpoint was a favorable neurological outcome at hospital discharge.

### RESULTS

Of the 432 unconscious adult patients who were treated with therapeutic hypothermia (32 °C to 34 °C) after ROSC, 144 whose blood ammonia level was measured on arrival at the emergency room were included. The quartiles of ammonia levels were a median of 79.5 µg/dl, and 25th and 75th percentile values of 47.5 µg/dl and 136.5 µg/dl, respectively.

A total of 82 (57.3%) of the 143 patients had favorable neurological outcomes. The ammonia level was lower among such patients than among those who had unfavorable neurological outcomes (a median, 72 µg/dl vs 110 µg/dl;  $p=0.0002$ ). Significant differences were seen in frequency of favorable neurological outcome among patients with the quartiles of ammonia levels (71% in the Q-1, 67% in the Q-2, 67% in the Q-3, 25% in the Q-4,  $p<0.001$ ), and the subgroups of patients with VF (67% in the Q-1, 71% in the Q-2, 33% in the Q-3, 15% in the Q-4,  $p=0.005$ ). A multiple logistic regression analysis showed that Q-4 of the quartiles of ammonia level was an independent predictor of unfavorable neurological outcomes with an adjusted odds ratio of 0.16 (95% CI, 0.051-0.522,  $p=0.0022$ ).

### CONCLUSION

High level of ammonia on ER arrival was associated with poor neurological outcome for patients treated with therapeutic hypothermia. Ammonia provides useful predictive neurological information before induction of hypothermia.

Ammonia as a Biochemical Marker of Neurological Outcomes for Patients Treated with Therapeutic Hypothermia after Out-of-Hospital Cardiac Arrest

The Japanese PULSE Hypothermia Study (J-PULSE Hypothermia) Group

Asuka Kasai, Ken Nagao,

## Background

Therapeutic hypothermia should be part of standardized treatment strategy for comatose survivors of cardiac arrest.

Excessive accumulation of ammonia induces neuronal metabolic derangements, promotes astrocyte swelling and perturbs cerebral nitric oxide metabolism.

Although studies have shown there is a correlation between increase in blood ammonia levels and hepatic encephalopathy, few data are available for patients treated with therapeutic hypothermia after out-of-hospital cardiac arrest.

## Hypotheses

There is a correlation between the blood  $\text{NH}_3$  levels and a favorable neurological outcome at hospital discharge.

The hyperammonia is associated with resuscitation outcomes in patients with out-of-hospital cardiac arrest treated with therapeutic hypothermia.

## Methods

### Study Patients

#### Inclusion Criteria

Adults patients who were treated with therapeutic hypothermia after return of spontaneous circulation (ROSC) from out-of-hospital cardiac arrest due to cardiac etiology.

#### Exclusion criteria

1. Age < 18 years
2. A lack of blood sample
3. Families refused to provide informed consent

## Study Organization

### Principle Investigator:

Hiroshi Nonogi

### Working members:

Ken Nagao, Hiroyuki Yokoyama, Yoshio Tahara, Shinichi Shirai, Shunji Kasaoka, Kazunori Kashiwase, Yuichi Motomura, Tomotaka Sawano, Mamoru Hase, Yuji Yasuga, Nobuaki Kokubu, Naoyuki Ohtani, Hideaki Arimoto, Yasuhiro Kuroda, Hiroshi Hazul

### Bio statisticians:

Naohiro Yonemoto, Akiko Kada

### Participating institution:

National Cerebral and Cardiovascular Center Sapporo Medical University Hospital

Nihon University Surugadai Hospital

Osaka Police Hospital  
Saga University Hospital

Hiroshima City Hospital



Yokohama City University

Kokura Memorial Hospital  
Saiseikai Senri Hospital

Osaka City General Hospital

AHA2011 採択者

	Session Type	Title
白井 伸一	ReSS - Sunday	Impact of Emergency Recanalization and Mild Hypothermia Therapy: Analysis of ST Segment of Electrocardiogram Following Recovery of Spontaneous Circulation After Cardiac Arrest
田原 良雄	ReSS - Saturday	Relation between Electrocardiographic Changes and Neurologic Outcomes in Patients Treated with Hypothermia after Out-of-hospital Ventricular Fibrillation Cardiac Arrest: J-PULSE-Hypo Registry.
松崎 真和	AHA - Tuesday	Effects of Rapid Intravenous Ice-Cold Fluids for Patients Treated with Therapeutic Hypothermia
國分 宣明	AHA - Tuesday	Cooling Duration and Rewarming Speed in Therapeutic Hypothermia for Out-of-hospital Cardiac Arrests: How Should We Combine the Protocols?
有元 秀樹	AHA - Tuesday	Does Neuromuscular Blocking Agent Help for Therapeutic Hypothermia? Results of a Multicenter Registry Study in Japan: J-PULSE-Hypo Registry
蘇我 孟群	ReSS - Saturday	Influence of Early Return of Spontaneous Circulation and Early Induction of Cooling on Neurological Outcome in Patients Treated with Therapeutic Hypothermia after Out-of-Hospital Shockable Cardiac Arrest Control Number: 11479
米本 直裕	AHA	The Impact of Bystander CPR on Defibrillation-Survival curve in Out-of-hospital Cardiac Arrest From All-Japan Utstein Registry Data
	ReSS - Saturday	Influence of Age Differences for Collapse-defibrillator Time on Survival in Out-of-Hospital Cardiac Arrest From All-Japan Utstein Registry Data
清水 直樹	ReSS - Saturday	Nationwide Epidemiology and Outcomes from Paediatric Out-of-Hospital Cardiac Arrest in Japan: From JCS-ReSS Research Group
嘉田 晃子	AHA	A Nationwide Survey of the Effects of the Accessibility of Emergency Medical Systems on Cardiovascular Mortality
吉川 圭	AHA	Effect of Cardiopulmonary Resuscitation Training on Favorable Neurological Outcome for In-Hospital Cardiac Arrest
黒澤 茶茶	ReSS - Sunday	International Comparison of Paediatric In-Hospital Cardiac Arrest - Impact of Critical Care Settings for Hospital Safety and Outcome: From the Japanese Registry of CPR for In-Hospital Cardiac Arrest(J-RCPR)

## Impact of Emergency Recanalization and Mild Hypothermia Therapy: Analysis of ST Segment of Electrocardiogram Following Recovery of Spontaneous Circulation After Cardiac Arrest

Shinichi Shirai, Kokura Memorial Hospital

Ken Nagao, Nihon University

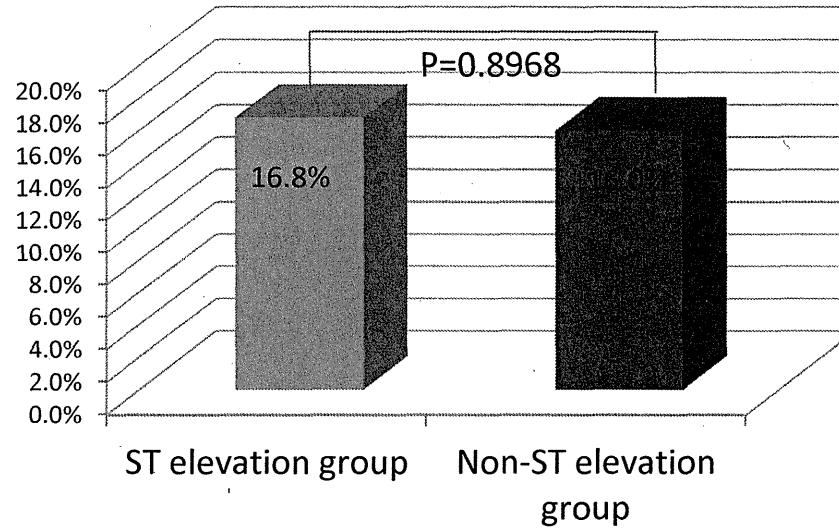
Naohiro Yonemoto, Hiroyuki Yokoyama, Hiroshi Nonogi, National Cardiovascular Center  
and J-PULSE-Hypo Investigators.

(Background) Recently published guideline recommended emergency angiography with prompt recanalization in the patients with ST elevation myocardial infarction (STEMI) as class I indication following recovery of spontaneous circulation (ROSC) after cardiac arrest, however, the recanalization in the absence of clearly defined STEMI after ROSC was not yet definitely recommended. The purpose of this study was to evaluate mortality and favorable neurologic outcomes (cerebral performance category [CPC] 1 and 2) at 30 days between the pts with ST elevation and those without ST elevation of electrocardiogram (ECG) immediately after ROSC undergoing percutaneous coronary intervention (PCI) with mild hypothermia (MHT). (Method) Data over a five-year period (2005-2009) were obtained for 452 pts treated with MHT from a multicenter registry in Japan. Of these patients, the 145 pts (who can be obtained ECG after ROSC) were diagnosed with acute ischemia by emergency angiography immediately after ROSC, and were subsequently treated with MHT and PCI. (Result) The 145 pts were divided into two groups based on the ECG after ROSC; ST elevation groups (STE) (n=95): ST elevation (n=94) and CLBBB (n=1), and Non ST elevation groups (NSTEMI) (n=50): ST depression (n=26), equivocal due to wide QRS complex (n=14), and almost normal ECG (n=10). Mortality rates at 30 days were 16.8% in STE group and 16.0% in NSTEMI group (p=0.8968). Favorable outcome rates at 30 days were 60.0% in STE group and 66.0% (p=0.4791) in NSTEMI group. (Conclusion) PCI with MHT were equally effective for 30 days mortality and favorable neurologic outcome for the pts with any ST segment type of ECG immediately after ROSC.

### Key Word

Hypothermia, Acute coronary Syndrome, Percutaneous coronary intervention, Sudden cardiac death, STEMI

### Mortality rates



### Favorable outcome rates

