

# Resuscitative Value of B-Type Natriuretic Peptide in Comatose Survivors Treated With Hypothermia After Out-of-Hospital Cardiac Arrest due to Cardiac Causes

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**Background** Two randomized studies have shown a neurological benefit of therapeutic hypothermia in comatose survivors after out-of-hospital cardiac arrest, but there are no studies of the cardiac neurohormone of B-type natriuretic peptide (BNP) in patients treated with hypothermia.

**Methods and Results** A prospective study was conducted of 109 comatose patients who were treated with mild hypothermia after out-of-hospital sudden cardiac arrest due to cardiac causes and whose BNP level was measured on arrival at the emergency room. The primary endpoint was a favorable neurological outcome at the time of hospital discharge. A total of 45 of the 109 patients had a favorable neurological outcome. The unadjusted rate of a favorable neurological outcome decreased in a stepwise fashion among patients in increasing quartiles of BNP level ( $p < 0.001$ ) and this association remained significant in subgroups of patients. The BNP cutoff value of 80 pg/ml for a favorable neurological outcome had an accuracy of 87.2%. In the multiple logistic-regression analysis, a BNP level of 80 pg/ml or less was an independent predictor of favorable neurological outcome.

**Conclusions** The measurement of BNP was found to provide valuable information regarding the neurological outcome of comatose survivors treated with mild hypothermia after out-of-hospital cardiac arrest due to cardiac causes. (*Circ J* 2007; 71: 370–376)

**Key Words:** Cardiac arrest; Cardiopulmonary resuscitation; Hypothermia; Natriuretic peptide

**B**-type natriuretic peptide (BNP) is a cardiac neurohormone synthesized in the ventricular myocardium and secreted as a response to ventricular expansion and pressure overload.<sup>1,2</sup> It acts on the failing heart through diuresis, natriuresis, inhibition of sympathetic nerve activity and vasodilation.<sup>3,4</sup> The serum level of this peptide is elevated in patients with heart failure or acute coronary syndrome, and correlates with the degree of left ventricular dysfunction, and the prognosis.<sup>5–12</sup> In addition, our recent study demonstrated that the BNP level had a resuscitative value in patients who were treated with standard cardiopulmonary resuscitation (CPR) after out-of-hospital cardiac arrest due to cardiac causes.<sup>13</sup> However, there are no clinical studies of the BNP level in patients treated with hypothermia after cardiac arrest due to cardiac causes.

In 2002 2 randomized studies of mild therapeutic hypothermia after out-of-hospital cardiac arrest showed a neurological benefit with a low risk of complications<sup>14,15</sup> and on the basis of those studies, the International Liaison Committee on Resuscitation recommended that unconscious adult

patients with spontaneous circulation 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), and that similar cooling could be considered for unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from any other rhythm or after cardiac arrest in hospital.<sup>16</sup> Since January 1996 we have also performed mild therapeutic hypothermia in comatose survivors of out-of-hospital cardiac arrest<sup>17,18</sup> but although the frequency of a favorable neurological outcome was similar to that in the 2 randomized studies, approximately half of all patients treated with mild hypothermia in these 3 studies had an unfavorable neurological outcome.<sup>14,15,18</sup>

We therefore decided to evaluate the BNP level to clarify whether or not it can distinguish a favorable neurological outcome from an unfavorable neurological outcome in comatose survivors treated with hypothermia after out-of-hospital cardiac arrest due to cardiac causes.

## Methods

### Study Patients

Patients transported to the emergency room after out-of-hospital cardiac arrest were enrolled if the following criteria were fulfilled: (1) aged between 18 and 74 years, (2) a witnessed sudden cardiac arrest, (3) an estimated interval of 15 min or less from the collapse to the first attempt at CPR by emergency life-saving technicians, (4) VF or pulseless

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**Table 1** Baseline Clinical Characteristics According to the Quartile of BNP Level\*

	Quartile 1 (2.0–30.4 pg/ml)	Quartile 2 (30.5–119 pg/ml)	Quartile 3 (119.1–278 pg/ml)	Quartile 4 (278.1–1,510 pg/ml)	p value for trend
No. of patients	27	27	28	27	
Age (years)					0.13
Median	58	58	61	63	
Interquartile range	49–61	50–63	55–66	53–66	
Male sex, n (%)	25 (92.6)	22 (81.5)	24 (85.7)	24 (88.9)	0.66
Location of collapse, n (%)					0.44
Home	2 (7.4)	3 (11.1)	4 (14.3)	6 (22.2)	
Public	25 (92.6)	24 (88.9)	24 (85.7)	21 (77.8)	
CPR instituted by bystanders, n (%)	16 (59.3)	14 (51.9)	15 (53.6)	15 (55.6)	0.95
Initial cardiac rhythm, n (%)					0.54
VF or pulseless VT	22 (81.5)	22 (81.5)	25 (89.3)	25 (92.6)	
PEA or asystole	5 (18.5)	5 (18.5)	3 (10.7)	2 (7.4)	
History of heart disease, n (%)	2 (7.4)	2 (7.4)	8 (28.6)	12 (44.4)	0.001
Time interval from event to event (min)					
Collapse to EMS call	3.0±1.1	2.8±1.2	2.9±1.0	3.0±1.1	0.93
EMS call to EMS arrival	5.6±1.4	5.8±1.1	6.0±1.2	5.9±1.6	0.77
EMS call to first defibrillatory shock <sup>§</sup>	9.6±2.1	9.6±1.9	9.4±1.9	9.2±2.1	0.92
EMS call to ER arrival	31.6±7.9	31.8±5.3	32.4±7.3	32.6±5.8	0.93
Collapse to ROSC	41.7±18.9	52.0±22.6	62.4±23.6	63.4±22.6	<0.001
ROSC before ER arrival, n (%)	7 (25.9)	4 (14.8)	2 (7.1)	1 (3.7)	0.07
Cardiac resuscitation					
Total epinephrine dose (mg)	1.4±0.9	1.7±0.7	1.9±0.5	1.9±0.4	0.06
Emergency CPB, n (%)	4 (14.8)	11 (40.7)	17 (60.7)	16 (59.3)	0.002
IABP, n (%)	20 (74.1)	22 (81.5)	22 (78.6)	26 (96.3)	0.16
Arrest due to ACS, n (%)	26 (96.3)	23 (85.3)	22 (78.6)	21 (77.8)	0.22
Coronary revascularization, n (%)	22 (81.5)	20 (74.1)	22 (78.6)	21 (77.8)	0.93
Mild therapeutic hypothermia					
Time interval from ER arrival to 34°C (h)	5.5±0.7	5.6±0.8	5.5±0.9	5.3±1.1	0.70
Core temperature at 48 h (°C) <sup>‡</sup>	34.0±0.2	34.0±0.2	34.0±0.2	34.2±0.2	0.98
Duration of cooling (h) <sup>‡</sup>	64.4±10.7	67.4±9.1	67.5±10.4	70.1±5.2	0.16

\*Mean ± SD.

BNP, B-type natriuretic peptide; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; EMS, emergency medical service; ER, emergency room; ROSC, return of spontaneous circulation; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon counterpulsation; ACS, acute coronary syndrome.

<sup>§</sup>Data are from patients whose initial rhythm was VF or pulseless VT and do not include patients whose initial rhythm was pulseless electrical activity or asystole.<sup>‡</sup>Data were available for 108 patients, because 1 patient died of post-resuscitation syndrome with cardiovascular dysfunction on day 1.

ventricular tachycardia (VF/pVT) as the recorded cardiac rhythm in the prehospital care, (5) a presumed cardiac origin of the arrest accorded to the Utstein Style reporting guidelines,<sup>19</sup> and (6) persistent coma after return of spontaneous circulation (ROSC) with standard or invasive CPR. The exclusion criteria were a tympanic-membrane temperature below 30°C on arrival at the emergency room, cardiogenic shock after ROSC (systolic blood pressure <90 mmHg despite pharmacological therapy and circulatory assistance with intra-aortic balloon counterpulsation and/or cardiopulmonary bypass), pregnancy, Glasgow-Pittsburgh overall performance category of 2 (moderate overall disability), 3 (several overall disability), or 4 (vegetative state)<sup>19,20</sup> before cardiac arrest or chronic renal failure with hemodialysis before cardiac arrest. Patients were also excluded if their families refused to give informed consent to participate in the study.

### Hypothermia Protocol

The patients who met the study criteria was treated with mild hypothermia as reported previously.<sup>17,18</sup> Mild hypothermia (34°C for 2 days or more, fundamentally for 3 days) by extracorporeal cooling method was immediately induced in comatose survivors whose systolic blood pressure increased to above 90 mmHg after achievement of ROSC by standard or invasive CPR with emergency cardiopulmonary bypass and intra-aortic balloon counterpulsation. Pulmonary arterial blood temperature was monitored continuously

as the core temperature by pulmonary artery catheter and the target of hypothermia therapy was to reach a target temperature of 34°C within 6 h of arrival at the emergency room, and maintain it for at least 2 days (fundamentally for 3 days). Rewarming was conducted slowly and gradually and took at least 3 days (warming by 0.5°C every 12 h then maintained at 35°C for 24 h).

### Data Collection

Blood samples to measure the BNP level were taken from a vein before drug administration in the emergency room. The specimens were immediately transferred to chilled disposable tubes containing an anticoagulant (disodium ethylenediamine tetraacetic acid) and then centrifuged for 10 min at 4°C. The plasma was frozen and stored at -80°C until analysis. Plasma BNP was then measured using a highly sensitive radioimmunoassay kit, Shionoria BNP (Shionogi Co, Ltd).<sup>13,18</sup> Resuscitation attempts by both emergency life-saving technicians and attending physicians were documented in accordance with a single data collection form (inclusive of the data according to the Utstein Style reporting guidelines,<sup>19,20</sup> information of past history from the family and/or the medical record before cardiac arrest, and treatment and clinical findings after arrival at the emergency room).

### Study Endpoints

The primary endpoint was a favorable neurological out-

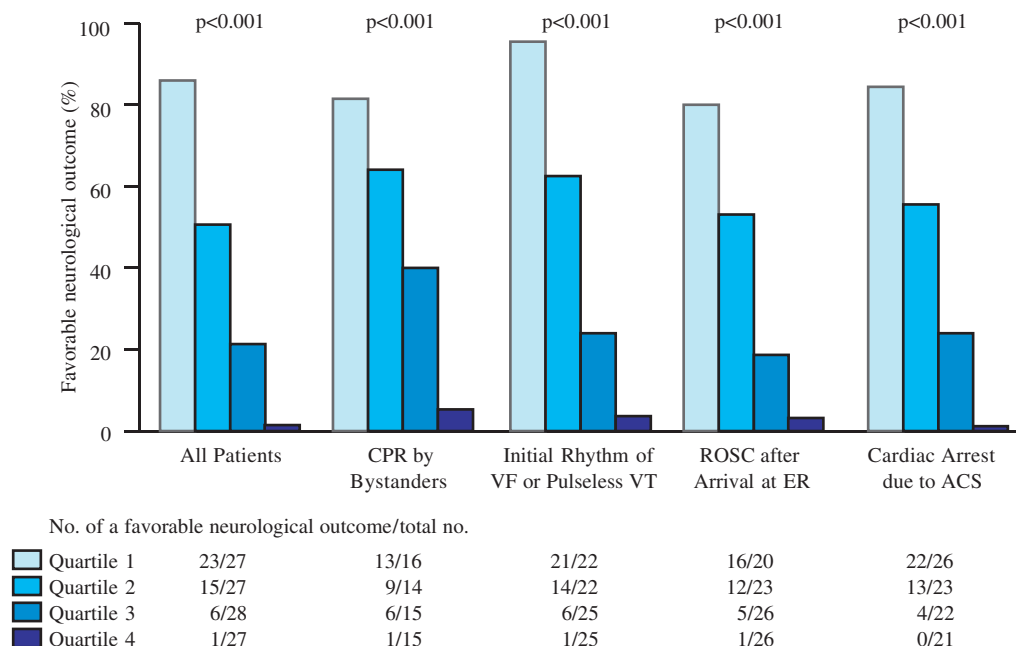


Fig 1. Association between the B-type natriuretic peptide (BNP) level and the frequency of a favorable neurological outcome (primary endpoint) in all study patients and in selected subgroups. The range of BNP levels was as follows: 2.0 to 30.4 pg/ml (quartile 1), 30.5 to 119 pg/ml (quartile 2), 119.1 to 278 pg/ml (quartile 3), and 278.1 to 1,510 pg/ml (quartile 4). A favorable neurological outcome was defined as a cerebral performance category of 1 (good performance) and 2 (moderate disability). ACS, acute coronary syndrome; CPR, cardiopulmonary resuscitation; ER, emergency room; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

come at the time of 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 are 3 (severe disability), 4 (vegetative state), and 5 (death)<sup>19,20</sup> The neurological outcome was assessed by physicians without any knowledge of the study. The secondary endpoints were survival to hospital discharge (Glasgow-Pittsburgh cerebral performance category of 1, 2, 3, or 4) or primary cause of death. The cause of death was defined as post-resuscitation syndromes (ie, cardiovascular dysfunction, neurological injury and serious infection complicated by multiple organ dysfunction)<sup>20</sup> or serious complication of invasive CPR.

#### Statistical Analysis

The patients were divided into 4 groups according to the quartiles of BNP level on arrival at the emergency room. The mean values and proportions of the baseline variables were compared among the quartiles using the Kruskal-Wallis rank-sum test for continuous variables, and the chi-square test for categorical variables, as appropriate. The chi-square test was used to evaluate the association between the quartiles of BNP level and both the primary and secondary endpoints. We constructed a receiver-operating characteristic curve to illustrate the various cutoff values of BNP. Finally, the independent factors associated with the primary endpoint were estimated from a multiple logistic regression model. All analyses were performed using SPSS software (version 11.0; Chicago, IL, USA).

## Results

#### Patients' Characteristics

Between January 1996 and December 2001, 822 of

49,838 patients who suffered an out-of-hospital cardiac arrest in Tokyo were transported to the emergency room of Surugadai Nihon University Hospital. A total of 110 patients, including the 23 patients in our pilot study,<sup>7</sup> were eligible for enrollment. The data for 1 of those patients was excluded from the analysis because he was registered as an unidentified victim. BNP levels of the remaining 109 patients ranged from 2 to 1,510 pg/ml, with a mean ( $\pm$ SD) of  $227 \pm 301$  pg/ml, a median of 119 pg/ml, and 25th and 75th percentile values of 30.4 pg/ml and 278 pg/ml, respectively. The mean ( $\pm$ SD) time interval from collapse to enrollment was  $42.1 \pm 6.4$  min (median, 43.0 min).

Table 1 shows the patients' characteristics. In general, the 4 groups of patients according to the quartiles of BNP level had similar baseline characteristics, but patients with higher BNP levels were more likely to have a history of heart disease, to have a longer interval between collapse and ROSC, and to require invasive CPR with emergency cardiopulmonary bypass than those with lower BNP levels.

#### Outcomes

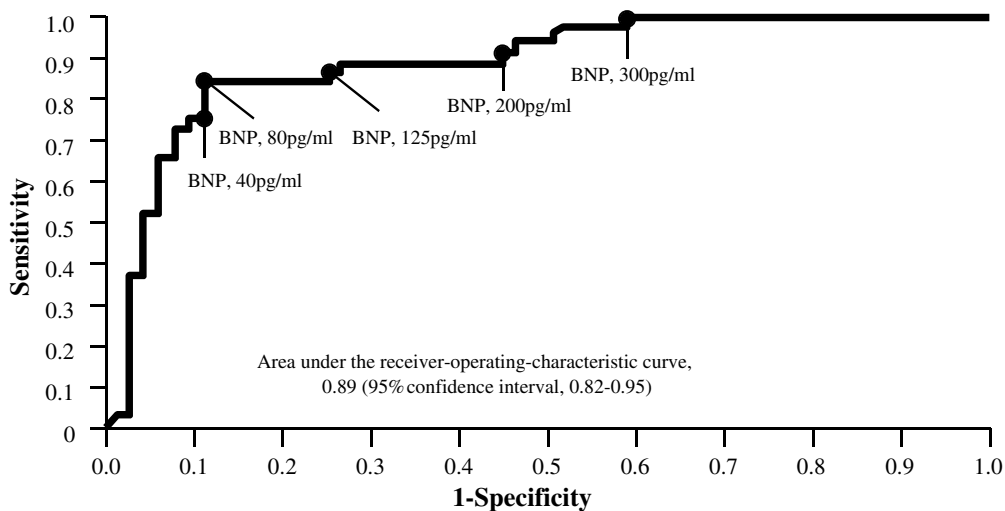
A total of 45 (41.3%) of the 109 patients had a favorable neurological outcome at the time of hospital discharge, and the BNP level was lower among such patients than among those who had an unfavorable neurological outcome (median, 30 pg/ml vs 243 pg/ml;  $p < 0.001$ ).

The primary endpoint of a favorable neurological outcome at the time of hospital discharge among all study patients decreased in stepwise fashion across the increasing quartiles of BNP level (with quartile 1 at 85.2% vs quartile 2 at 55.6% vs quartile 3 at 21.4% vs quartile 4 at 3.7%). This association remained significant among the subgroups of patients with bystander-instigated CPR, VF/pVT as the initial cardiac rhythm, ROSC after arrival at the emergency

**Table 2 Secondary Outcomes According to the Quartile of BNP Level**

	Quartile 1 (2.0–30.4 pg/ml)	Quartile 2 (30.5–119 pg/ml)	Quartile 3 (119.1–278 pg/ml)	Quartile 4 (278.1–1,510 pg/ml)	<i>p</i> value for trend
No. of patients	27	27	28	27	
Survival to hospital discharge, <i>n</i> (%)	24 (88.9)	18 (66.7)	10 (35.7)	5 (18.5)	<0.001
Cause of death ( <i>n</i> )					0.18
Cardiovascular dysfunction	0	5	9	14	
Neurological injury	2	3	7	6	
Serious infection	0	0	2	2	
Serious complication of invasive cardiopulmonary resuscitation	1	1	0	0	

Abbreviation see in Table 1.



BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
		(95% confidence interval)			
40	73 (67-81)	89 (86-92)	83 (78-88)	83 (78-88)	83
80	84 (81-88)	89 (87-92)	84 (81-88)	89 (87-92)	87
125	87 (83-91)	73 (67-81)	70 (62-78)	89 (85-92)	79
200	91 (88-95)	55 (43-70)	59 (47-73)	90 (86-94)	70
300	100	38 (25-57)	53 (41-69)	100	63

Fig 2. Receiver-operating-characteristic curve for various cutoff levels of B-type natriuretic peptide (BNP) to differentiate a favorable neurological outcome and an unfavorable neurological outcome at the time of hospital discharge. A favorable neurological outcome was defined as a cerebral performance category of 1 (good performance) and 2 (moderate disability), and an unfavorable neurological outcome was defined as a cerebral performance category of 3 (severe disability), 4 (a vegetative state), and 5 (death).

room, and cardiac arrest due to acute coronary syndrome ( $p < 0.001$ , respectively) (Fig 1).

The secondary endpoint of survival to hospital discharge also decreased in stepwise fashion across the increasing quartiles of BNP level ( $p < 0.001$ ) (Table 2). Of 52 patients who died in hospital, the primary cause of death was considered to be cardiovascular dysfunction in 25 (48.1%) (deaths occurred between 1 and 37 days after admission to hospital), neurological injury in 21 (40.4%) (deaths occurred between 3 and 24 days after admission), serious infection in 4 (7.7%) (deaths occurred between 14 and 35 days after admission), and serious complication of invasive CPR in 2 (3.8%) (serious bleeding due to vessel injury at the cardiopulmonary bypass insertion site on day 3 and day 4, respectively). There was no significant difference among patients according to the quartiles of BNP level regarding cause of

death, although the number of patients who died of cardiovascular dysfunction increased in stepwise fashion across the increasing quartiles of BNP level.

#### Evaluation of BNP

The area under the ROC curve was 0.89 (95% confidence interval, 0.82–0.95;  $p < 0.001$ ) (Fig 2). A BNP cutoff value of 80 pg/ml had the highest combined sensitivity and specificity with an accuracy of 87.2% for identification of a favorable neurological outcome at the time of hospital discharge. Higher values were associated with more accurate negative predictive values (for a BNP value of 300 pg/ml, the negative predictive value was 100%).

In the multiple logistic regression analysis for independent predictors of a favorable neurological outcome at the time of hospital discharge, which included age, gender,

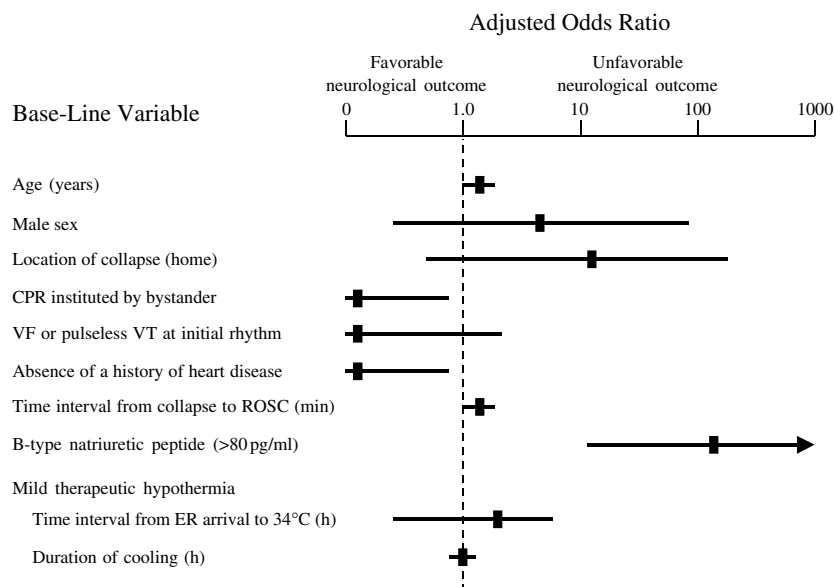


Fig 3. Adjusted odds ratios for a favorable neurological outcome at the time of hospital discharge according to selected factors, from the multiple logistic-regression analysis. A favorable neurological outcome was defined as a cerebral performance category of 1 (good performance) and 2 (moderate disability) and an unfavorable neurological outcome was defined as a cerebral performance category of 3 (severe disability), 4 (a vegetative state), and 5 (death). Horizontal lines are 95% confidence intervals. Data were available for 108 patients, because one patient died of postresuscitation syndrome with cardiovascular dysfunction on day 1. CPR, cardiopulmonary resuscitation; ER, emergency room; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.

location of collapse (home vs public place), presence or absence of bystander-instigated CPR, initial recorded cardiac rhythm (VF/pVT vs pulseless electrical activity or asystole), presence or absence of a history of heart disease, time interval from collapse to ROSC, BNP level ( $\leq 80$  pg/ml vs  $>80$  pg/ml), time interval from emergency room arrival to attainment of a core temperature at  $34^{\circ}\text{C}$  and duration of cooling stage, a BNP value of more than 80 pg/ml was the strongest independent predictor of an unfavorable neurological outcome, with an adjusted odds ratio of 131 (95% confidence interval, 11–1,584). Other independent predictors were bystander-instigated CPR, a history of heart disease and time interval from collapse to ROSC (Fig 3).

## Discussion

To our knowledge this is the first clinical report that the BNP level on arrival at the emergency room can be used to predict neurological outcome in patients treated with mild hypothermia after sudden cardiac arrest due to cardiac causes. The unadjusted rate of a favorable neurological outcome at the time of hospital discharge decreased in a step-wise fashion in increasing quartiles of BNP level and this association remained significant in subgroups of patients (Fig 1). The BNP cutoff value of 80 pg/ml for a favorable neurological outcome had an accuracy of 87.2% (Fig 2). In the multiple logistic regression analysis, a BNP level of 80 pg/ml or less was one of the independent predictors of a favorable neurological outcome (Fig 3). In addition, a BNP level of 300 pg/ml or more had a negative predictive of 100% for favorable neurological outcome (Fig 2).

Recent studies demonstrate that BNP is a sensitive marker of ventricular damage and dysfunction and is a window to the heart<sup>1–12</sup> In the clinical studies myocardial ischemia augments the synthesis and release of BNP, even in the absence of myocardial necrosis or preexisting left ventricular dysfunction, although the level of expression of the BNP gene in the left ventricle tripled within 4 h of coronary ligation in an animal model<sup>25–28</sup> In the present study, we measured the BNP level once, approximately 43 min after cardiac arrest. The BNP level was significantly higher among patients with a history of heart disease than among

those without such a history (median 291 pg/ml vs 74 pg/ml,  $p<0.001$ ) and the patients with higher BNP levels were more likely to have a history of heart disease than those with lower BNP levels. However, the patients without a history of heart disease accounted for 56% of the quartile 4 of BNP levels and for 71% of the quartile 3 of BNP levels. In addition, our previous study showed that patients with out-of-hospital cardiac arrest due to cardiac causes had a significantly higher BNP level on arrival at the emergency room compared with those with non-cardiac causes (median 137 pg/ml vs 13 pg/ml,  $p<0.001$ )<sup>29</sup> Thus we considered that the BNP level on arrival at the emergency room after sudden cardiac arrest was related to not only the degree of pre-existing ventricular dysfunction but also to the degree of ventricular dysfunction after sudden cardiac arrest and/or onset of acute coronary syndrome. These findings suggest that the higher the stress of ventricular wall tension, the greater concentration of BNP produced and released into the bloodstream on arrival at the emergency room in patients with out-of-hospital sudden cardiac arrest due to cardiac causes.

A healthy brain and a functional patient are the primary goals of CPR. Brain-oriented intensive care is essential. Following the ROSC, after a brief initial period of hyperemia, both cardiac output and cerebral blood flow decrease as a result of post-resuscitation syndrome with cardiovascular and microcirculatory dysfunction<sup>20</sup> After ROSC almost 50% of patients die of cardiovascular dysfunction within 24 h of the cardiac arrest. Microcirculatory dysfunction caused by multifocal hypoxia leads to rapid release of toxic enzymes and free radicals into the cerebrospinal fluid and blood<sup>20</sup> In the patients who are saved from death by cardiovascular dysfunction, the cerebral and microvascular abnormalities persisting as metabolic disorders progress over 1–3 days, and most patients die of neurological injury<sup>20</sup> Of the 52 patients who died in hospital in the present study, 28 deaths were caused by cardiovascular dysfunction and 18 were caused by neurological injury as the result of post-resuscitation syndrome. The BNP level on arrival at the emergency room was significantly higher among patients who died of post-resuscitation syndrome than among those who discharged alive with a favorable neurological out-



come. In addition, our recent study showed that the BNP level on arrival at the emergency room provides valuable information regarding admission to hospital, 24-h survival and survival to hospital discharge,<sup>13</sup> which suggests that the BNP level may predict the degree of post-resuscitation syndrome.

Vigilant attention to cardiovascular and microcirculatory dysfunction can significantly reduce the possibility of secondary neurological injury and maximize the chances of favorable neurological recovery.<sup>20,24</sup> Mild hypothermia reduces the cerebral metabolic need for oxygen and is thought to suppress many of the chemical reactions associated with reperfusion injury. On the other hand, adverse effects of therapeutic hypothermia include coagulopathy, cardiac dysrhythmias, impaired cardiac function, and increased susceptibility to infection.<sup>14–18,20–23</sup> The prevalence and severity of those adverse effects is proportional to the depth and duration of cooling. In the present study, a protocol of mild hypothermia was used, with a longer duration of cooling (34°C for 2 days or more, fundamentally for 3 days), because the criteria for induction of hypothermia included comatose survivors after out-of-hospital sudden cardiac arrest from any rhythm, and the procedure of cardiac resuscitation was to use invasive CPR with emergency cardiopulmonary bypass when ROSC could not be achieved by standard CPR. It is considered that the patients in this study presented with more severe conditions for resuscitation than those in the 2 previous randomized studies, because the time interval from collapse until ROSC in this study was longer than in the randomized studies (this study had a mean of 54.8 min and a median of 45 min, compared with the European study with a median of 22 min and the Australian study with a mean of 26.5 min).<sup>14,15,18</sup> However, there was no significant difference in the frequency of a favorable neurological outcome among patients treated with hypothermia in the 3 studies. Although the cooling period of 12–24 h in the 2 randomized studies was not associated with clinical significant adverse effects,<sup>14,15</sup> the patients treated with hypothermia (33°C for 12 h) in the Australian study had a lower cardiac index in the cooling stage than the patients treated with normothermia, and the cardiac index at a median of 2.1 L·min<sup>-1</sup>·m<sup>-2</sup> in the cooling stage indicated the frequency of a favorable neurological outcome to be 49%.<sup>15</sup> Our pilot study of mild hypothermia (34°C for 2 days or more, fundamentally for 3 days) showed that a cardiac index at 2.2 L·min<sup>-1</sup>·m<sup>-2</sup> or more in the cooling stage was one of the predictors of a good recovery!<sup>17</sup> These findings suggest that recovery of cerebral function is associated with cardiovascular function and microcirculation in the cooling stage of mild hypothermia after ROSC. Thus we consider that the BNP level on arrival at the emergency room may predict the degree of cardiovascular and microcirculatory dysfunction in the cooling stage of mild hypothermia.

The results of multiple logistic regression analysis showed that VF/pVT as the initial recorded cardiac rhythm was not an independent predictor of a favorable neurological outcome, but a BNP level of 80 pg/ml or less was one of the independent predictors. The cutoff point for BNP for a favorable neurological outcome in this study was similar to that for the long-term risk of death and cardiac events in a study of acute coronary syndrome<sup>8</sup> the diagnosis in studies of heart failure,<sup>7,9</sup> and the survival to hospital discharge in our recent study of out-of-hospital cardiac arrest<sup>13</sup> (this study involved 80 pg/ml vs the acute coronary syndrome

study's 80 pg/ml; whereas the heart failure studies involved 100 pg/ml vs our recent study's 100 pg/ml). Furthermore, the neurological outcome did not improve when the BNP level was 300 pg/ml or more. A BNP value of 80 pg/ml or 100 pg/ml may thus have a common threshold in the acute phase of heart conditions.

#### Study Limitations

This study was not comparative for therapeutic hypothermia after cardiac arrest, although we measured the BNP before initiating drug administration using a highly sensitive radioimmunoassay so that the attending physicians could be blinded to the resuscitation and post-resuscitation care procedures. If the indication and strategy of therapeutic hypothermia are investigated in detail, or if BNP is measured using a rapid (15-min) whole-blood assay,<sup>7,8,30</sup> after administration of epinephrine, or in the cooling stage of mild hypothermia, the cutoff point and upper limit of BNP for a favorable neurological outcome might change. In addition, our extracorporeal cooling method is efficient, but too invasive to perform in either a prehospital environment or in most emergency departments!<sup>6</sup>

In conclusion, the BNP level on arrival at the emergency room provides valuable information regarding neurological outcome in comatose survivors treated with mild hypothermia after sudden cardiac arrest due to cardiac causes. These results may extend the boundaries of the efficacy of therapeutic hypothermia for unconscious adult patients with spontaneous circulation after sudden cardiac arrest.

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