B-Type Natriuretic Peptide as a Marker of Resuscitation in Patients With Cardiac Arrest Outside the Hospital

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Background Although the circulating concentration of B-type natriuretic peptide (BNP) has both a prognostic and diagnostic value in heart disease, no data are available regarding its resuscitative value for out-of-hospital cardiac arrest.

Methods and Results The present study was a prospective study of 401 patients whose BNP was measured on arrival at the emergency room after an out-of-hospital cardiac arrest with a cardiac cause. The primary endpoint was survival to hospital discharge. The unadjusted rate of survival to hospital discharge decreased in a stepwise fashion among patients in increasing quartiles of BNP concentration ($p < 0.001$). After adjusting for independent predictors of resuscitation, the odds ratios for survival to hospital discharge in the second, third and fourth quartiles of BNP were 0.13 (95% confidence interval (CI), 0.04–0.46), 0.10 (95% CI, 0.03–0.41), and 0.004 (95% CI, 0.00–0.16), respectively. The BNP cutoff value of 100 pg/ml for survival had a sensitivity of 83% and a negative predictive value of 96%.

Conclusions The measurement of BNP was found to provide valuable predictive information for survival to hospital discharge in patients with out-of-hospital cardiac arrest of cardiac etiology. (*Circ J* 2004; 68: 477–482)

Key Words: Cardiac arrest; Cardiopulmonary resuscitation; Cardiovascular diseases; Natriuretic peptides; Survival

Achieving the optimal survival rate for out-of-hospital cardiac arrest in every community is the challenge now and in the future.^{1–3} Each year some 90,000 people in Japan and 225,000 in the United States and Europe suffer an out-of-hospital cardiac arrest, thus accounting for almost half of all deaths caused by cardiovascular disease.^{2–4} The 1-year survival rate after an out-of-hospital cardiac arrest of cardiac origin is extremely low (3%) in Japan,³ and although the chain of survival has been shown to have a significant relationship with survival,^{1–3,5} no clinical studies of the cardiac neurohormonal activation of B-type natriuretic peptide (BNP) are available for this cardiac event.

BNP is a cardiac neurohormone synthesized in the ventricular myocardium and secreted from the ventricle as a response to ventricular expansion and pressure overload.^{6–8} A-type, B-type and C-type natriuretic peptides are similar in their ability to promote natriuresis and diuresis, inhibit the renin–angiotensin–aldosterone axis and sympathetic activity, and act as vasodilators; however, BNP is a more sensitive and specific indicator of ventricular disorders than the other natriuretic peptides.^{9,10} Clinical studies of heart failure suggest that the BNP concentration can be used to confirm the diagnosis, measure the severity of left ventricu-

lar compromise, quantify the functional class, estimate the prognosis and predict future cardiac events, and to evaluate the efficacy of therapy.^{6–14} Furthermore, the BNP concentration is also useful for predicting the long-term risk of death and non-fatal cardiac events in patients with acute coronary syndrome (ACS).^{9,15,16}

We therefore hypothesized that the BNP concentration could discriminate between survival and death for patients with an out-of-hospital cardiac arrest of cardiac cause.

Methods

Tokyo Emergency Medical System

Tokyo has an area of 1,750 km², and its daytime and nighttime population in 2001 was estimated to be 14,410,382 and 11,609,869, respectively. Ambulance units of public emergency medical services in Tokyo consist of 3 emergency medical service personnel, at least one of whom is a licensed emergency life-saving technician. Emergency life-saving technicians are authorized by the Minister of Health, Labor and Welfare to treat cardiac arrest through maintenance of the airway using a laryngeal mask or an esophageal–tracheal combitube, intravenous infusion of extracellular fluid, and defibrillation using a semi-automated external defibrillator. Regulations applying to ambulance units for out-of-hospital cardiac arrest stipulate that emergency life-saving technicians cannot make the decision to stop cardiopulmonary resuscitation and are required to transport patients, excluding any obviously dead individuals, to the nearest emergency hospital. Consequently, more than 95% of patients with out-of-hospital cardiac arrest are transported under cardiopulmonary resuscitation by emergency medical service personnel each year.³ The rules of

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Table 1 Baseline Clinical Characteristics According to the Quartile of B-Type Natriuretic Peptide Concentration

	Quartile 1 (2.0–33.8 pg/ml)	Quartile 2 (33.9–152.0 pg/ml)	Quartile 3 (152.1–392.0 pg/ml)	Quartile 4 (392.1–2,620 pg/ml)	p value for trend
No. of patients	100	100	100	101	
Age, years	61.5±12.9	63.4±10.2	64.9±13.4	65.4±10.6	0.08
Male sex, %	80	78	84	79	0.7
Location, %					0.02
Home	22	33	37	43	
Public, indoors	39	34	31	33	
Public, outdoors	39	33	32	25	
Witnessed arrest, %	56	66	61	54	0.3
CPR by bystander, %	14	13	12	20	0.4
Call-response interval, min	5.2±3.1	5.9±2.7	5.7±2.2	5.3±2.7	0.3
Initial cardiac rhythm, %					0.003
VF or pulseless VT	52	38	33	31	
Pulseless electrical activity	10	10	7	8	
Asystole	38	52	60	61	
Call-to-ER interval, min	33.8±9.8	33.6±6.9	33.9±7.1	35.2±9.4	0.5
ROSC before ER, %	18	4	2	1	<0.001
Cause of arrest, %					
Suspected acute coronary syndrome	86	85	78	69	0.007
Treatment after ROSC, %					
Intra-aortic balloon counterpulsation	27	28	30	27	0.9
Coronary revascularization	40	34	30	27	0.2
Mild hypothermia	35	14	11	1	<0.001

Data, CPR, cardiopulmonary resuscitation; ER, emergency room; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia. Where applicable, data are mean ± SD.

the Tokyo medical examiner system for out-of-hospital cardiac arrest stipulate that coroners are required to examine the cause of death in patients who do not respond to treatment in the emergency hospital and whose attending physician has been unable to diagnose their disease.

Study Population

Patients who were transported to the emergency room after an out-of-hospital cardiac arrest were eligible to participate in the study. The inclusion criteria were: age more than 17 years, cardiac arrest prior to the arrival of emergency personnel, and presumed cardiac origin of the arrest according to the Utstein Style.¹⁷ Patients were excluded if they were treated by an emergency cardiopulmonary bypass after failing to respond to standard advanced cardiovascular life support according to the guidelines of the American Heart Association,^{1,5} if they had been treated by hemodialysis for chronic renal failure, or if their families refused to provide informed consent to participate in the study.

Data Collection and Treatment

Blood samples to measure the BNP concentration were taken from a vein before beginning drug administration in the emergency room. Blood was immediately transferred into chilled glass tubes containing an anti-coagulant (disodium ethylenediamine tetraacetic acid and aprotinin), centrifuged at 3,000 G for 10 min at 4°C, and the plasma was frozen and stored at –80°C until analysis. Plasma BNP was measured using the highly sensitive radioimmunoassay kit of Shiono RIA BNP (Shionogi Co, Ltd), as reported previously.⁶

After the return of spontaneous circulation with standard advanced cardiovascular life support according to the guidelines of the American Heart Association,^{1,5} intra-aortic balloon counterpulsation was immediately performed in patients with cardiogenic shock (a systolic blood pressure of less than 90 mmHg for at least 15 min despite pharmaco-

logical therapy, and a heart rate of more than 60 beats/min). In cases of suspected ACS, coronary revascularization was immediately performed if a Thrombolysis in Myocardial Infarction grade 0, 1 or 2 flow¹⁸ was observed in the relevant artery under emergency coronary angiography. Therapeutic hypothermia by coil cooling (34°C for more than 2 days) was subsequently performed in comatose survivors whose systolic blood pressure had increased to above 90 mmHg.¹⁹

The data on the cardiac arrest for individual patients were recorded according to the Utstein Style.¹⁷

Study Endpoints

The primary endpoint was survival to hospital discharge. The secondary endpoints were a return of spontaneous circulation, defined as the return of a spontaneous palpable pulse and blood pressure for at least 1 min;²⁰ admission to the hospital;¹⁷ a 24-h survival, or a favorable neurological outcome at the time of hospital discharge, defined as a Pittsburgh cerebral-performance category of 1 (good recovery) or 2 (moderate disability) on a 5-category scale.²¹

Statistical Analysis

The patients were divided into 4 groups according to quartiles of the BNP concentration on arrival at the emergency room. The mean values and proportions of the baseline variables were compared among the quartiles using a one-way analysis of variance for continuous variables, and the Kruskal-Wallis test for categorical variables. The Kruskal-Wallis test was used to evaluate the association between the quartiles of the BNP concentration in all patients, including subgroups of patients and the primary endpoint, and between the quartiles of BNP concentration in all patients and the secondary endpoints. The independent factors associated with the primary endpoint were estimated from a multiple logistic-regression model. Finally, we constructed a receiver-operating-characteristic curve to illustrate the various cutoff values of BNP.

Fig 1. Association between the B-type natriuretic peptide level and the rate of survival to hospital discharge (primary end point) in all patients and in selected subgroups. CPR, cardiopulmonary resuscitation; ER, emergency room; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia. The range of B-type natriuretic peptide levels was as follows: 2.0–33.8 pg/ml (quartile 1), 33.9–152.0 pg/ml (quartile 2), 152.1–392.0 pg/ml (quartile 3), and 392.1–2,620.0 pg/ml (quartile 4). P values are for the trend within each group.

Table 2 Secondary Outcomes According to the Quartile of B-Type Natriuretic Peptide Concentration

	Quartile 1 (2.0–33.8 pg/ml)	Quartile 2 (33.9–152.0 pg/ml)	Quartile 3 (152.1–392.0 pg/ml)	Quartile 4 (392.1–2,620 pg/ml)	p value for trend
No. of patients	100	100	100	101	
Return of spontaneous circulation, %	46	37	32	31	0.1
Admission to hospital, %	46	28	19	6	<0.001
24-h survival, %	42	20	13	4	<0.001
Favorable neurologic outcome*, %	33	8	4	0	<0.001

*A favorable neurologic outcome was defined as a cerebral-performance category of 1 (good recovery) or 2 (moderate disability).

Results

Patients Characteristics

Between January 1996 and December 2001, 822 of the 49,838 patients who suffered an out-of-hospital cardiac arrest in Tokyo were transported to the emergency room of our hospital. A total of 513 patients were assessed for eligibility: 112 met the exclusion criteria, thus 401 patients were enrolled in this study. The BNP concentrations ranged from 2 to 2,620 pg/ml, with a mean ($\pm$ SD) of 236 ± 283 pg/ml, a median of 152 pg/ml, and 25th and 75th percentile values of 33.8 and 392 pg/ml, respectively.

Patients with lower BNP concentrations were more likely than those with higher concentrations to have suffered cardiac arrest in a public place, to have suffered ventricular fibrillation or pulseless ventricular tachycardia in the initial cardiac rhythm, to have a return of spontaneous circulation before reaching the emergency room, and to be suspected of having ACS. The number of patients undergoing therapeutic hypothermia decreased in a stepwise fashion across the increasing quartiles of the BNP concentration ($p < 0.001$) (Table 1).

Outcomes

A total of 52 of the 401 patients survived to discharge from the hospital and the BNP concentration was lower among such patients than among those who died (mean $\pm$ SD, 74 ± 95 vs 260 ± 266 pg/ml; $p < 0.001$). The primary end-point of survival to hospital discharge in all patients decreased in a stepwise fashion across the increasing quartiles of the BNP concentration (with quartile 1 at 34% vs quartile 2 at 10% vs quartile 3 at 7% vs quartile 4 at 1%; $p < 0.001$). This association remained significant in the subgroups of patients with witnessed arrest, cardiopulmonary resuscitation instituted by a bystander, ventricular fibrillation or pulseless ventricular tachycardia in the initial cardiac rhythm, and a return of spontaneous circulation after arrival at the emergency room ($p < 0.001$, respectively) (Fig 1). The secondary endpoint of without a return of spontaneous circulation also decreased in a stepwise fashion across the increasing quartiles of the BNP concentration ($p < 0.001$, respectively) (Table 2). In the multiple logistic-regression analysis for independent predictors of survival, including age, gender, the presence or absence of witnessed arrest and cardiopulmonary resuscitation instituted by a bystander, the call-response interval, the initial cardiac rhythms at the scene, and the presence or absence

Fig2. Adjusted odds ratio for survival to hospital discharge according to selected factors, from the multiple logistic-regression analysis. Horizontal lines are 95% confidence intervals. CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; ROSC, return of spontaneous circulation.

BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	73 (67-81)	74 (67-81)	29 (20-42)	95 (93-96)	74
100	83 (78-88)	66 (58-75)	27 (18-39)	96 (95-97)	68
150	85 (80-90)	56 (45-69)	22 (13-38)	96 (95-98)	59
200	85 (78-92)	44 (29-66)	18 (8-43)	95 (93-98)	49
300	98 (97-99)	35 (23-54)	18 (9-37)	99 (99-100)	43
400	100	27 (15-49)	17 (8-38)	100	36

Fig3. Receiver-operating-characteristic curve for various cutoff levels of B-type natriuretic peptide (BNP) to differentiate survival from death in patients with out-of-hospital cardiac arrest due to cardiac causes.

of a return of spontaneous circulation before arrival at the emergency room, the increasing quartiles of the BNP concentration remained significantly associated with a decreased risk of survival to hospital discharge. The adjusted odds ratios for survival to hospital discharge in the

second, third and fourth quartiles of BNP concentration were 0.13 (95% confidence interval (CI), 0.04–0.46), 0.10 (95% CI, 0.03–0.41), and 0.004 (95% CI, 0.00–0.16), respectively (Fig2). When the age and call-response interval were entered into the model as continuous variables, the

results remained unchanged.

BNP Threshold

The capacity of BNP to differentiate survival to hospital discharge from death was assessed with a receiver-operating-characteristic (ROC) curve analysis (Fig 3). The area under the ROC curve was 0.80 (95% CI, 0.74–0.86; $p < 0.001$). The BNP cutoff value of 100 pg/ml had the highest combined sensitivity and specificity for the identification of survival to hospital discharge. Higher values were associated with more accurate negative predictive values (for a BNP value of 400 pg/ml, the negative predictive value was 100%). When a BNP cutoff value of 100 pg/ml was used in the former multiple logistic-regression model in place of the quartiles of BNP concentration, the results remained unchanged, and a value of 100 pg/ml or less was the second strongest, independent predictor of survival to hospital discharge, with an adjusted odds ratio of 13.0 (95% CI, 4.4–38.3).

Discussion

The present study demonstrated that the BNP concentration on arrival at the emergency room provides valuable information for risk stratification of patients with out-of-hospital cardiac arrest of cardiac origin. Increasing concentrations of BNP were predictive of an increased risk of death in hospital and unfavorable neurologic outcomes at the time of hospital discharge. A multiple logistic-regression analysis showed BNP to be a strong independent factor in survival to hospital discharge. Finally, we determined the optimal cutoff point for BNP regarding survival to hospital discharge to be 100 pg/ml.

Despite the absence of studies evaluating the BNP concentrations in patients with out-of-hospital cardiac arrest, 2 large-scale studies of BNP have been reported.^{11,16} One is a study of the prognostic value of BNP in patients with ACS¹⁶ in which a total of 2,525 patients with ACS were divided into quartiles based on their BNP concentrations within the first few days after the onset of ischemic symptoms. The BNP concentrations ranged from 5 to 1,456 pg/ml with a median of 81 pg/ml, and a high concentration of BNP was associated with an increased long-term risk of death and non-fatal cardiac events. Our study patients were also divided into quartiles according to their BNP concentrations on arrival at the emergency room, but their BNP concentrations differed from those in the study of ACS because it was presumed that 21% (83/401) of the present patients suffered from other heart disease including heart failure without ACS, hypertrophic cardiomyopathy, myocarditis, electrophysiological cardiac arrest etc. Moreover, the time interval from onset to enrollment into the study was shorter in the present study than that in the patients with ACS. Although the level of expression of the BNP gene in the left ventricle tripled within 4 h of a coronary ligation in an animal model,²² the BNP concentration increased rapidly and transiently after exercise testing in patients with stable angina, after uncomplicated percutaneous transluminal coronary angioplasty, and after the onset of unstable angina.^{23–26}

We measured the BNP concentration once, within approximately 1 h of the cardiac arrest, and it is not possible to determine whether BNP is reflective of sudden cardiac arrest or of a pre-existing ventricular dysfunction from a single measurement. Half of the patients who die of acute

myocardial infarction do so before reaching a hospital and in most of these deaths the presenting rhythm is ventricular fibrillation.^{27–30} In the patients who were suspected to have ACS in the present study, a low concentration of BNP may indicate that the time interval from the onset of ischemic symptoms to the incidence of primary ventricular fibrillation, which occurs during the first few hours of the onset as an acute electrical event, is short. On the other hand, a high concentration of BNP may indicate that the interval is long or that secondary ventricular fibrillation, which is associated with heart failure or cardiogenic shock complicating ACS, has occurred.

In a previous study of out-of-hospital cardiac arrest,³¹ we observed significantly different concentrations of BNP on arrival at the emergency room between patients with cardiac causes and those with non-cardiac causes (a median of 137 pg/ml in the cardiac cases vs 13 pg/ml in the non-cardiac cases, $p < 0.001$). These findings suggest that the higher the stress of ventricular wall tension, the greater the concentration of BNP produced and released into the bloodstream on arrival at the emergency department.

Two large-scale studies reported the BNP threshold to be 80 pg/ml for the long-term risk of death in ACS,¹⁶ and 100 pg/ml for the diagnosis of congestive heart failure.¹¹ We also evaluated the cutoff point for survival to hospital discharge and found that concentrations of 100 pg/ml or less for BNP were a strong, independent predictor of survival. Furthermore, no patients whose BNP concentration had increased 400 pg/ml or more survived to discharge from hospital. A BNP value of 80–100 pg/ml may thus have a common threshold in the acute phase of heart disease.

Patients with lower BNP concentrations were more likely than those with higher concentrations to undergo therapeutic hypothermia after return of spontaneous circulation. Shock after return of spontaneous circulation was one of the exclusion criteria of therapeutic hypothermia in the 2 randomized clinical studies,^{4,32,33} which was similar to the criteria of therapeutic hypothermia in the present study. Our recent study of therapeutic hypothermia after return of spontaneous circulation showed the BNP concentration to be one of the predictors of a favorable neurologic outcome.³⁴ The results of the present study suggest that the BNP concentration may be a useful marker of resuscitation in patients with out-of-hospital cardiac arrest of cardiac origin.

Study Limitations

It was not multicenter study for cardiopulmonary resuscitation after out-of-hospital cardiac arrest. The frequency of survival to hospital discharge in the present study, which included patients treated with intra-aortic balloon counterpulsation, coronary revascularization or mild hypothermia, was higher than that in Japanese multicenter studies^{35–37} of treatment with standard cardiopulmonary resuscitation. If the cause of the cardiac arrest or the cardiac resuscitation treatment and postresuscitation care are investigated in detail, or if BNP is measured using a rapid (15-min) whole-blood assay,¹¹ the cutoff point and upper limit of BNP concentration for survival to hospital discharge might change slightly.

In conclusion, we found that the concentration of BNP on arrival at the emergency room after an out-of-hospital cardiac arrest of cardiac origin can provide valuable information regarding the risk stratification of survival, a result that extends the utility of measuring the BNP concentration.

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