Prognostic Value of Plasma Brain Natriuretic Peptide Combined With Left Ventricular Dimensions in Predicting Sudden Death of Patients With Chronic Heart Failure

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ABSTRACT

Background: We evaluated a combined assessment of brain natriuretic peptide (BNP) with left ventricular dimensions as a prognostic marker for sudden death in patients with chronic heart failure (CHF). Ventricular dimensions and BNP are separately recognized as prognostic markers for sudden death in patients with CHF.

Methods and Results: CHF patients at Stage C and B were registered for a prospective study. From the database, we analyzed 417 patients with coronary arterial disease (CAD) or primary/secondary dilated cardiomyopathy (DCM). Main effects of BNP, left ventricular ejection fraction (EF), LV diastolic dimension (LVDD), and interaction of BNP with the EF and LVDD were tested with Cox's proportional hazard model. BNP in sudden death patients was significantly higher than that in event-free patients. Although multivariate analysis revealed that BNP by itself was not an independent risk factor for sudden death after adjustments, it was revealed that BNP entered the model via interaction with EF as a risk factor associating with sudden death. On the other hand, BNP was an independent risk factor associating with heart failure events (death and hospitalization), and BNP did not enter the model via an interaction with EF.

Conclusion: BNP by itself was an independent risk factor for the heart failure events, but not for sudden death in CHF patients of the present study. However, BNP should be important in predicting sudden death when measured with EF.

Key Words: Chronic heart failure, brain natriuretic peptide, left ventricular dimensions, sudden death.

Brain natriuretic peptide (BNP) is recognized as a powerful prognostic marker for patients with chronic heart failure (CHF).[1–3] BNP was reported to predict not only heart failure events, but also sudden cardiac death in patients with CHF.[4] Troughton et al[5] reported that BNP-guided therapy was superior to conventional methods including echocardiography. Berger et al[4] clearly demonstrated that BNP was a useful marker of sudden death in CHF patients with systolic dysfunction (left ventricular ejection fraction [LVEF] $<35\%$). However, sudden death occurs not only in patients with severe systolic dysfunction, but also in patients with mild systolic dysfunction or preserved systolic function.[3,6] Several electrocardiogram markers for sudden death in CHF patients have been proposed,[7–10] but none has been established.

Recently, Richard et al[11] reported that plasma BNP and LVEF are complementary, independent predictors, and their combined use improved the risk stratification of patients after myocardial infarction. This concept can likely be applied to CHF patients and may improve the risk stratification for sudden death. The present study was designed to test the hypothesis that a combined assessment of BNP with left ventricular dimensions can work as a prognostic marker for sudden death in patients with CHF. For this purpose, we analyzed our CHF database (CHART, Chronic Heart failure Analysis and Registration in Tohoku district). CHART is a prospective study including a hospital-based cohort of CHF patients.[3]

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Methods

Organization of the CHART Study

The organization of the CHART study was described elsewhere.[3] Patients with the following clinical findings of heart failure were eligible for the registration: (1) patients with certain organic heart disease and a documented history of clinical congestive heart failure defined by the Framingham criteria,[12] (2) patients with organic heart disease whose echocardiographic ejection fraction (EF) with the Teicholz formula for M-mode recordings was 50% or less, and (3) patients with organic heart disease whose echocardiographic left ventricular diastolic dimension (LVDD) was 55 mm or more. The CHART study was designed to reflect most CHF patients in the real clinical situation. Thus the CHART included not only patients with systolic dysfunction, but also patients with preserved systolic function, because all such patients may have some risk for sudden death. This was a multicenter prospective observational study, which included CHF patients who showed a stable condition for more than 3 weeks and met at least 1 of the above criteria. The CHART was approved by the local ethics committees.

The etiologies of CHF were divided into 5 categories (ie, dilated cardiomyopathy [DCM], coronary artery disease [CAD], valvular heart disease [VHD] left ventricular hypertrophy [LVH], and other heart diseases). DCM included both primary and secondary dilated cardiomyopathies, but not "ischemic cardiomyopathy." CAD included "ischemic cardiomyopathy." VHD was diagnosed mainly by the patient's history and echocardiographic findings. LVH included hypertensive heart disease and idiopathic hypertrophic cardiomyopathy. The other heart diseases mainly included congenital or unclassified heart diseases.

Echocardiographic measurements were required within 3 months of the stable period before or after the registration. The BNP measurement was recommended at the registration and measured by RIA with Shionoria (CIS, France) BNP. The individual investigator assessed the New York Heart Association (NYHA) functional classification and comorbidity according to the present status and medical records. Nonsustained ventricular tachycardia (NSVT) was defined as 3 or more consecutive ventricular premature beats (RR intervals ≤400 milliseconds) that were not sustained for more than 30 seconds. NSVT was diagnosed by Holter electrocardiogram recording that was performed within 3 months of the stable period before or after registration.

Data Analysis

The comparison of the incidence of events between the groups was performed by the chi-square test. Differences in mean values (age, BNP, EF) were tested by analysis of variance (1-way) and multiple comparison was performed by the method of Bonferroni without adjustment. The causes of death were categorized as heart failure death, sudden death, and other causes. Sudden death was defined as sudden unexpected death without worsening heart failure. It included witnessed sudden collapses and deaths, and unwitnessed deaths that were unexpected and not explained by noncardiac causes. Heart failure death was defined as death from an exacerbation of CHF. All hospitalization events involving an exacerbation of congestive symptoms were included as the hospitalization events. In the survival analysis of sudden death, non–sudden death patients were censored at the time of the death. The prognoses of patients with CHF were evaluated by Kaplan-Meier survival curve analysis and the log-rank test. Cox multivariate regression analysis was performed to evaluate the predictive value. Significant variables, which should be included in the Cox model, were determined by the incrementally stepwise method. The endpoints were total death, sudden death, heart failure death, and combined heart failure events (heart failure death and hospitalization). The following variables were tested: age, sex, history of heart failure hospitalization, NYHA functional class, diabetes, hypertension, NSVT, atrial fibrillation, drugs (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, β-blocker, digitalis, aldosterone receptor blockers, nitrates, and Ca^{2+} channel blocker), log BNP, LVEF, and LVDD. Also, interactions of EF/log BNP, and LVDD/log BNP were tested. The Cox analysis was computed using package software, StatView 5.0 (SAS, Cary, North Carolina).

Results

In the present study, we analyzed 417 patients who had underlying heart diseases of CAD or DCM and in whom the BNP measurements and echocardiography were available at the registration. Table 1 summarizes the basic characteristics of the patients grouped by the outcomes. During the mean follow-up of 26 months, we observed 16 heart failure deaths, 30 sudden unexpected deaths, and 20 noncardiac deaths. Fifty-eight patients were hospitalized because of exacerbations of heart failure. The ages of patients who experienced heart failure hospitalization were significantly greater than those of event-free patients. No significant difference was found in the gender distribution.

EF of the sudden, unexpected death group was lower than that of the event-free patients. LVDD of patients who developed heart failure death and of those of the sudden death groups was significantly greater than that of event-free patients. The incidence of NYHA III/IV was significantly greater in patients who developed heart failure events, including both death and hospitalization. The incidence of diabetes was greater in patients who developed sudden death.

Figure 1 shows the distribution of patients on the BNP-EF or BNP-LVDD planes. BNP was converted to logarithmic value.[4] No significant linear correlation was found between log BNP and LVEF and log BNP and LVDD. Cardiac events including heart failure deaths; sudden, unexpected deaths; and heart failure hospitalization are indicated. To examine the prognostic value of BNP combined with the echocardiographic measurements, patients were divided into 4 subgroups by the median values of log BNP (≥2.12 or <2.12) and either EF (≤38 or >38 %) or LVDD (≥59 or <59 mm).

In Cox's proportional regression analysis with the stepwise method, significant factors entered the model are summarized in Table 2. In the analysis for sudden death, log BNP ≥2.12 entered the model via an interaction with EF ≤38%. Also, NSVT and β-blocker entered the model. However, the main effects of EF ≤38 and log BNP ≥2.12 did not enter the model. In regard to the combined heart failure events, the main effects of log BNP ≥2.12, LVDD ≥59, age, NYHA III/IV, and previous heart failure hospitalization entered the model, but log BNP ≥2.12 did not enter the model via an interaction with EF or LVDD.

Figure 2 shows the Kaplan-Meyer analysis for patients grouped by EF and log BNP. The incidence of sudden death

Table 1. Basic Characteristics of Patients

	Total	Event-Free	Sudden, Unexpected Death	Heart Failure Death	Heart Failure Hospitalization	Noncardiac Death
Number of cases	417	293	30	16	58	20
Age	64 ± 14	63 ± 14	63 ± 14	69 ± 12	69 ± 13*	73 ± 14
Male gender (%)	69.4	72.8	67.9	81.3	71.9	85.0
Coronary artery diseases (%)	48.2	45.6	57.1	50.0	57.9	80.0
NYHA III/IV (%)	19.3	16.0	25.0	62.5	31.6	15.0
Brain natriuretic peptide (pg/mL)	274 ± 380	211 ± 277	569 ± 776*	512 ± 574**	370 ± 353**	343 ± 482
Ejection fraction (%)	38 ± 12	39 ± 11	29 ± 10*	34 ± 11	37 ± 12	42 ± 12
LV diastolic dimension (mm)	59 ± 9	59 ± 8	65 ± 11**	67 ± 10**	60 ± 9	57 ± 8
Diabetes (%)	22.4	17.7	35.7	37.5	24.6	55.0
β-blocker (%)	43.4	48.0	21.4	18.8	40.4	35.0
ACEI/ARB (%)	77.1	79.3	75.0	50.0	80.7	60.0

NYHA, New York Heart Association; LV, Left Ventricular; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
*$P < .05$.
**$P < .01$.

in patients with EF ≤38% and log BNP ≥2.12 was significantly more frequent than that in patients with EF >38%. The incidence of combined heart failure events in patients with EF ≤38% and log BNP ≥2.12 was significantly more frequent than that in patients with log BNP <2.12.

Discussion

The present data suggest that BNP is an independent risk factor for the combined heart failure events, but not for sudden death in either a continuous or binary form. However, BNP should be important in predicting sudden death when measured with EF. Thus patients with high BNP and preserved systolic function showed low risk for sudden death, but high risk for heart failure events.

Combined Assessment Of BNP With LV Dimensions for Risk Stratification in Patients With CHF

The mean value of BNP in sudden death patients was significantly higher that that in event-free patients, although Cox multivariate analysis did not reveal the significance of BNP. Thus the predictive value of BNP for sudden death appeared to be obscure in the present study.

Berger et al[4] reported that BNP was a powerful predictor for sudden death in patients with CHF. Their study was performed in patients with EF <35%; thus, the difference should come from population differences. The present data indicated that log BNP entered the model via an interaction with EF (Table 2). Thus both data indicated that the predictive value of BNP for sudden death should be interpreted with the EF data. BNP was an independent risk factor for

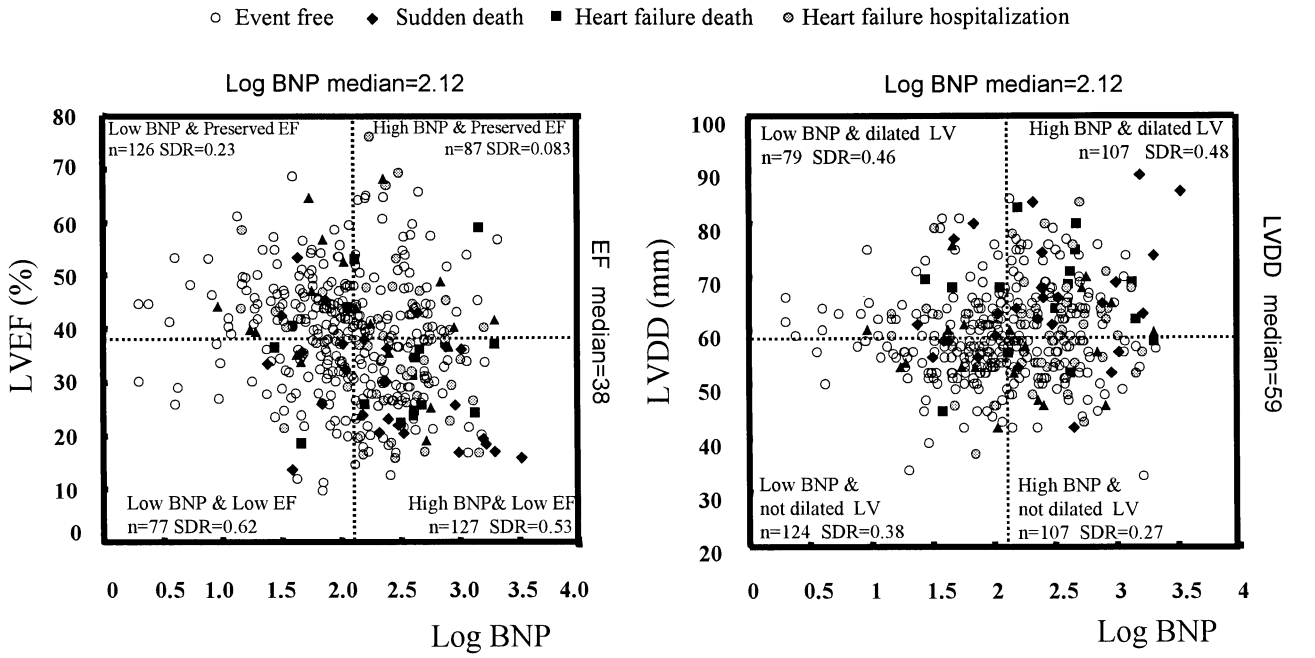

Fig. 1. EF and LVDD (Y axis) are plotted to log BNP (X axis). No linear relationship was found between them. Patients were divided into 4 groups by median values of BNP and either LVEF or LVDD. BNP, brain natriuretic peptide; EF, ejection fraction; LVDD, left ventricular diastolic dimension. SDR = Sudden death rate (sudden death/total death) in each subgroup.

Table 2. Hazard Ratio and 95% Confidence Interval by Cox Proportional Regression Analysis

	Predictors	Hazard Ratio	95% Confidence Interval		*P*
Total death	Age	1.04	1.01	1.07	.0049
	NYHA III/IV	2.46	1.36	4.49	.0032
	Dilated LV	3.00	1.69	5.32	.0002
	Diabetes	4.21	2.41	7.41	<.0001
	NSVT	2.50	1.46	4.34	.0010
	ACEI/ARB	0.46	0.24	0.86	.0112
Sudden, unexpected death	High BNP and low EF	3.46	1.39	7.94	.0054
	NSVT	4.41	1.84	10.57	.0009
	β-blocker	0.32	0.12	0.87	.0248
Heart failure death/ hospitalization	Age	1.03	1.01	1.06	.0047
	NYHA III/IV	2.06	1.20	3.54	.0069
	Previous HF hosp.	2.18	1.24	3.85	.0069
	Dilated LV	1.79	1.07	2.99	.0265
	High BNP	2.10	1.14	3.85	.0168

NYHA, New York Heart Association functional class; previous HF hosp. Previous hospitalization from congestive heart failure; high BNP, brain natriuretic peptide >132 pg/mL; low EF, ejection fraction <38%; dilated LV, left ventricular end-diastolic dimension >59 mm; ACEI/ARB angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; NSVT, nonsustained ventricular tachycardia. These significant variables were determined by the stepwise methods.

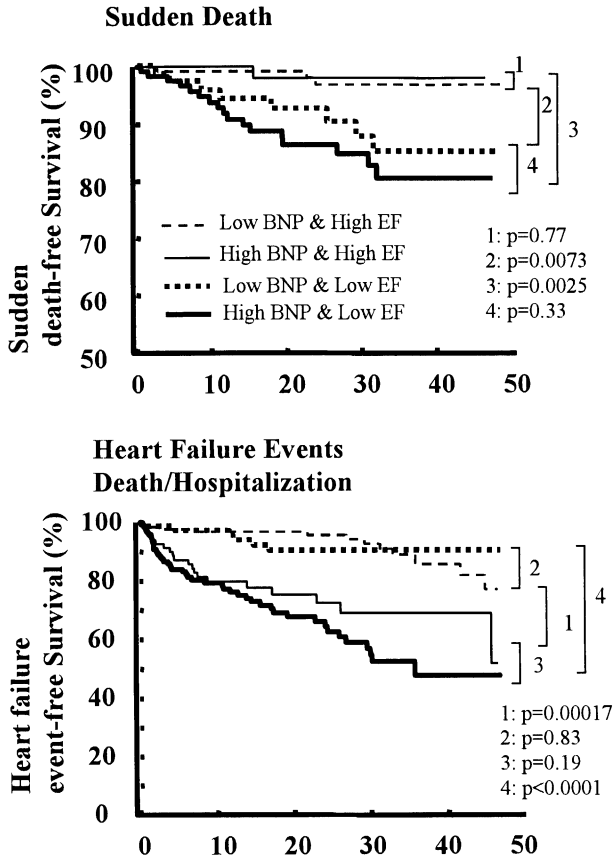

Fig. 2. Kaplan-Meyer survival curves for sudden death (upper panel) and combined heart failure events (lower panel). Patients were divided into 4 groups by log BNP ≥2.12 or <2.12 combined with EF ≤38% or >38%. Log rank test for all groups combined revealed that the chi-square value was 23.62 ($P < .0001$) in the sudden death analysis and 57.33 ($P < .0001$) in the heart failure events analysis. The multiple comparisons are indicated in the figure.

the combined heart failure events, but not for sudden death in the present CHF population—including not only patients with systolic dysfunction, but also patients with preserved systolic function. The prognosis was similar despite the mode of heart failure.[14,15]

Richard et al[6] recently reported that BNP and EF are complementary, independent predictors of the prognosis after myocardial infarction. Our data partially support that their concept can be applied to patients with CHF. The interaction of log BNP-EF entered the model, although the main effects of log BNP did not. Thus BNP is not an independent risk factor, but is important when measured with EF.

As shown in Fig. 2, absolute incidence of sudden death in patients with preserved systolic function was relatively low regardless of BNP level. However, sudden death accounted for 25% of total death (4/25) in patients with preserved systolic function, as shown in Fig. 1.

We speculate that CHF-related sudden death will frequently occur in patients who have progressed cardiac remodeling together with increased ventricular stretch. This is consistent with the fundamental dogma that sudden death in CHF is caused mainly by ventricular tachycardia or fibrillation. It is well known that most BNP is ventricular in origin and released in proportion to ventricular stretch,[16,17] and basic studies have shown that myocardial stretch, especially in damaged myocardium, can cause a run of ventricular premature beats.[18] On the other hand, heart failure events are mainly caused by increased ventricular overload, which is a major determinant of the BNP level in both types of heart failure—systolic and diastolic dysfunction.

Limitations

The present study has several limitations. First, the incidence of sudden death was relatively low (30/417 for 26 months), which may be partially explained by the severity of the patients, although the proportion of sudden death over total deaths (49%) was not lower compared with previous studies[19] in Europe and the United States. We recruited patients without previous hospitalization due to heart failure if they met the LV dimension criteria. It is important to prevent sudden death in those patients, as 9 out of 30 sudden deaths occurred in those patients. We assessed the LV dimensions by echocardiography, which may be unreliable, especially in patients with previous myocardial infarction. However, an alternative method, such as radionuclide ventriculography, is available only in large-scale medical centers. Also, recent randomized trials[18–20] have employed echocardiographic measurements in CHF patients with CAD.

Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers entered the model for total death, and β-blocker entered the model for sudden death. The effects of

these medications were demonstrated in larger randomized trials. Although the present data support the effectiveness of these medications, we must interpret this carefully because this study was not randomized and there may have been unrecognized differences. Moreover, the kinds of agents and their doses were not controlled. The present data provided encouraging results, but not conclusive ones. In the present study, we adopted median values as the cutoff value for dividing patients into 4 subgroups. Consequently, the cutoff point of BNP (log BNP $\geq$2.12) was consistent with that of a previous study,[4] and the cutoff points of EF ($\leq$38%) and LVDD ($\geq$59 mm) were consistent with those of the eligible criteria for previous randomized studies.[20–22] However, the cutoff point may vary with the CHF population. The interpretations of the present study are based on the measurements taken at the registration. Therefore, it remains unknown whether time-dependent changes in BNP or LV dimensions can improve or exacerbate the prognosis of patients with CHF. It was reported in the Valsartan Heart Failure Trial trial[23] that changes in plasma BNP are related to the prognosis of patients with CHF. Because there are numerous unsolved questions concerning the risk stratification of patients with CHF, a large-scale prospective study should be conducted.

Conclusions

The present findings indicate that BNP was not an independent risk factor for sudden death, but should be important when measured with EF. BNP was an independent risk factor for the combine heart failure events. The therapeutic strategy should be planned according to the risk stratification of individual patients, and their responses to the therapy should be verified according to the improvement in the risk factors such as EF and BNP.

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Appendix

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