Clinical practice

Serial measurements associated with an amelioration of acute heart failure: an analysis of repeated quantification of plasma BNP levels

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Abstract

Background: The magnitude of improvement of acute heart failure achieved during treatment varies greatly among patients. We examined changes in the plasma B-type natriuretic peptide (BNP) levels of patients with acute heart failure and attempted to elucidate the clinical factors associated with amelioration of acute heart failure.

Methods and results: The study population consisted of 208 consecutive patients admitted to our institution with acute heart failure. We measured plasma BNP levels before and after treatment of acute heart failure and evaluated these levels based on median age, body mass index (BMI), creatinine (Cr) level, and left ventricular ejection fraction (EF). Plasma BNP levels before treatment were equivalent between the younger and older age groups; however, plasma BNP levels after treatment were higher in the older age group ($p<0.01$). Plasma BNP levels before treatment were significantly high in the lower BMI group ($p<0.05$) and the higher Cr group ($p<0.01$). Similarly, plasma BNP levels after treatment were high in both the lower BMI and higher Cr groups ($p<0.01$ for both). In the low EF group, plasma BNP levels before treatment were significantly high ($p<0.01$), while plasma BNP levels after treatment were equivalent to those in the high EF group. A multiple linear regression analysis revealed that Cr was positively correlated and BMI and EF were negatively correlated with plasma BNP levels before treatment; however, the contributions of age, BMI, and Cr in reducing plasma BNP levels were more significant after treatment.

Conclusions: The contributions of clinical factors working against amelioration of heart failure vary before and after treatment. Regarding plasma BNP levels, older age, very low BMI, and the presence of renal dysfunction eventually act to prevent amelioration of acute heart failure. Systolic dysfunction does not act against amelioration of acute heart failure.

Introduction

Therapeutic advances in drug development and mechanical support have made the treatment of patients with severe acute heart failure possible. However, in some patients, acute heart failure can be improved only slightly, even with intensive treatment. Various reasons exist to explain the resistance in improvement of acute heart failure. For instance, severe deterioration of cardiac function, including

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systolic and diastolic dysfunction, is naturally a primary cause. Other clinical factors, including age, body mass index (BMI), and renal function, could also be involved. However, to date, the clinical factors acting against the changes in plasma BNP levels that occur with amelioration of acute heart failure have not been clarified.

B-type (brain) natriuretic peptide (BNP) is a hormone that was identified in 1988.[1] Plasma BNP levels rise as heart failure becomes more severe. Plasma BNP levels have therefore been utilized for early detection of heart failure and to estimate disease severity and predict prognoses.[2–14] In the present study, we attempted to elucidate the clinical factors associated with amelioration of acute heart failure by evaluating serial measurements of plasma BNP levels at admission and after treatment of acute heart failure. We used serial BNP measurements because the outcomes of patients with acute heart failure can be predicted using these measurements.[3,6–10]

Methods

Study patients

The study population consisted of 208 consecutive patients hospitalized due to heart failure between 1 January 2007 and 31 March 2010 at Jikei University Hospital (there were 183, 171, and 174 heart failure patients in 2007, 2008, and 2009, respectively, and there are 33 beds in the cardiology ward, including six beds in the coronary care unit).

Plasma BNP levels were measured twice: once during admission and again after intensive treatment of acute heart failure. We excluded patients with myocardial infarction because plasma BNP levels noticeably and rapidly increase during the 24 hours after its onset in a monophasic manner, then transiently decrease, possibly followed by another increase 2−3 days after onset (depending on the degree of ventricular remodelling), thus resulting in a biphasic profile.[11] Patients who required emergency surgery, including coronary aorta bypass surgery and non-cardiac surgery, during the period between the collection of the first and second plasma BNP samples were also excluded. The study protocol [21−015 (5593)] was approved by the Ethics Committee of The Jikei University School of Medicine.

Diagnosis of acute heart failure

Acute heart failure was diagnosed according to the guidelines for treatment of acute heart failure published by the Japanese Circulation Society. The patients with heart failure symptoms [New York Heart Association (NYHA) functional classes II−IV] underwent several examinations (blood gas analysis, blood sampling, electrocardiogram, plain chest radiograph, echocardiogram) and decided to be admitted to our hospital.

Treatment of acute heart failure

The patients were treated with drugs, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, beta-blockers, nitrates, carperitide (human atrial natriuretic peptide), and, if necessary, catecholamines and mechanical supports such as respirators, intra-aortic balloon pumping, or percutaneous cardiopulmonary support.

Blood sampling and measurement of plasma BNP levels

We measured plasma BNP levels immediately after admission (before intensive treatment) and at the time of improvement of acute heart failure (after intensive treatment). In each case, a second sample was collected when the clinical symptoms of acute heart failure improved and the patient's condition stabilized. Whole blood (5 ml) was collected in tubes containing potassium EDTA (1 mg/ml blood). Plasma BNP was measured with a rapid enzyme-linked immunosorbent assay (non-extracted) using an antibody to human BNP (Shionogi, Tokyo, Japan). Serum biochemical analyses of creatinine (Cr) was performed in a central laboratory in our hospital during the study. In order to determine the effects of clinical factors on changes in plasma BNP levels, we divided the patients into two groups based on median age (72.5 years, interquartile range, IQR, 59.0–82.3 years), median BMI (23.4 kg/m², IQR 21.2–25.6 kg/m²), median Cr level (1.20 mg/dl, IQR 0.90–1.64 mg/dl), and median left ventricular ejection fraction, EF, (39.2%, IQR 28.3–51.9%).

Echocardiographic examination and other measurements

An echocardiographic examination was performed in all patients by three expert cardiologists. EF was used as a marker of systolic left ventricular dysfunction. On the basis of height and weight at admission, BMI was calculated as the weight divided by the square of the height.

Main outcome measures

The main outcome measures were major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, stroke, heart failure, and all-cause mortality.

Statistical analysis

The continuous variables are expressed as the mean±SD or the median. The data of two groups were compared using the Wilcoxon signed-rank test or the Mann−Whitney *U*-test, as appropriate. Age, BMI, Cr, and EF were analysed by quintiles of plasma BNP levels, and the values of each

quintile were compared with those of the lowest 20% using the Mann−Whitney *U*-test. Multiple regression analyses were performed when multiple values were compared. According to a multivariate analysis, natural log transformation was performed on BNP values because they were not normally distributed. The clinical factors affecting reduction of plasma BNP levels after treatment to <200 pg/ml were examined using a multiple logistic regression analysis. It has been suggested that the plasma BNP threshold level critical for predicting prognoses is approximately 180–200 pg/ml.[11] It is thus generally believed that reducing BNP levels is preferable and that ensuring that plasma BNP levels are <200 pg/ml after treatment of acute heart failure is beneficial for improving prognosis.

All statistical analyses were performed using SPSS version 11.5J (SPSS Japan, Tokyo, Japan), and differences were considered to be statistically significant for *p*-values <0.05.

Results

Study population

The baseline characteristics of the study population are shown in Table 1. No patients died during therapy and the clinical symptoms of acute heart failure were successively improved by intensive treatment, although the remediation levels varied among the patients. This study included 44 patients (21.2% overall) in NYHA functional class II, 44 patients (21.2% overall) in class III, and 120 patients (57.7% overall) in class IV.

Changes in plasma BNP levels after treatment

Plasma BNP levels were observed to decrease after treatment in all patients (Figure 1). The mean±SD and median plasma BNP levels were 1043.8±1011.7 and 739.1 pg/ml (IQR 395.6–1334.0 pg/ml) before treatment and decreased significantly to 331.7±334.1 and 204.3 pg/ml (IQR 116.9–424.6 pg/ml) after treatment, respectively (*p*<0.01). The mean interval±SD between the first and second blood sample collections was 42.4±56.7 days.

Changing plasma BNP levels affected by clinical factors

Figure 2 and Table 2 show the changes in plasma BNP levels before and after treatment according to the medians of the clinical factors. Plasma BNP levels before treatment were equivalent between the older and younger age groups (not significant); however, plasma BNP levels after treatment were significantly higher in the older age group (*p*<0.01). Plasma BNP levels were significantly higher in the low BMI group than in the high BMI group both before

**Table 1.** Baseline characteristics of the study population.

Clinical characteristic	Population (*n*=208)
Age (years)	69.9±15.0
Body mass index (kg/m^2)	23.8±4.4
BNP <200 pg/ml before treatment	17 (8.2)[a]
Creatinine (mg/dl)	1.6±1.7
Ejection fraction (%)	40.9±15.9
Male/female (*n/n*, % female)	148/60 (28.8)
Recovery period of BNP (days)	42.4±56.7
Underlying heart disease	
Ischaemic heart disease	54 (26.0)
Hypertension	50 (24.0)
Atrial fibrillation	34 (16.3)
Dilated cardiomyopathy	31 (14.9)
Valvular heart disease	18 (8.7)
Other myocardiopathy[b]	10 (4.8)
Complete atrioventricular block	5 (2.4)
Congenital heart disease	4 (1.9)
Constrictive pericarditis	2 (1.0)
Hyperlipidaemia	70 (33.7)
Type 2 diabetes mellitus	67 (32.2)
Drugs	
ACE/ARB	182 (87.5)
Beta-blocker	115 (55.3)
Ca-blocker	105 (50.5)
Digoxin	39 (18.8)
Diuretics	187 (89.9)
Statins	50 (24.0)

Values are *n* (%) or mean±SD, unless otherwise stated.
[a]Mean±SD BNP in these patients was 142.4±52.4 pg/ml.
[b]Other includes patients with chest pain syndrome, pre-operating checks, or others.
ACE/ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BNP, B-type natriuretic peptide.
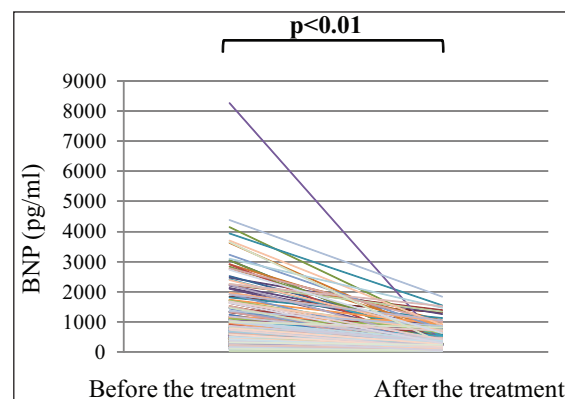
Figure 1. Changes in plasma B-type natriuretic peptide (BNP) levels before and after treatment in the entire study population.

(*p*<0.05) and after treatment (*p*<0.01). Plasma BNP levels before treatment were significantly high in the low EF group compared to those in the high EF group (*p*<0.01); however, plasma BNP levels after treatment in both groups
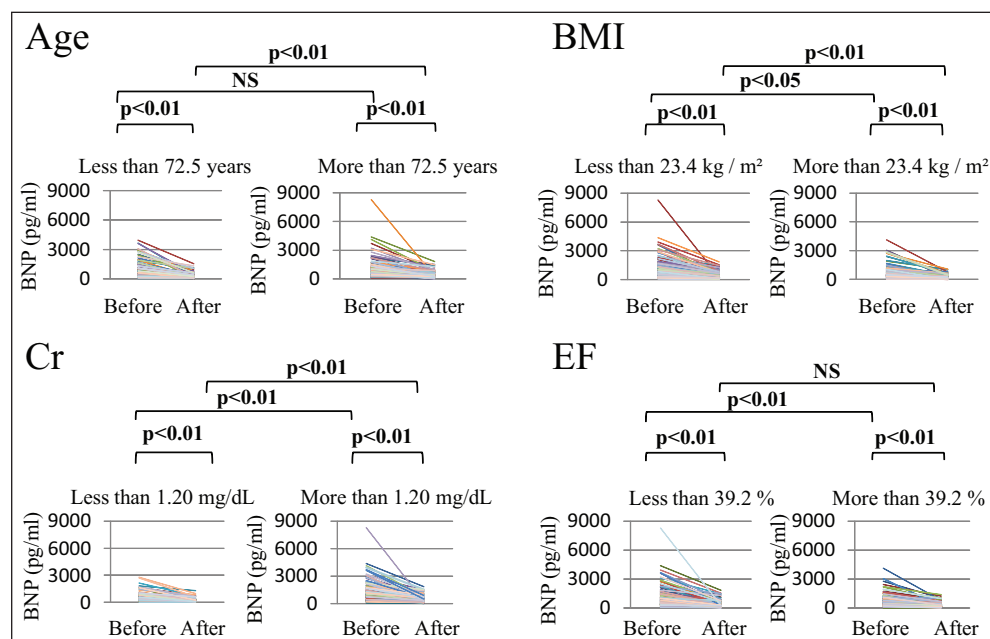
Figure 2. Changes in plasma BNP levels before and after treatment classified on the basis of median age, BMI, creatinine, and ejection fraction.

The leftmost graph of each pair are for below the median of each clinical factor and the rightmost for above the median.

BMI, Body mass index; BNP, B-type natriuretic peptide; Cr, creatinine; EF, ejection fraction.

**Table 2.** Changing plasma B-type natriuretic peptidelevels affected by clinical factors.

Clinical factor	n (%)	Before	After	Before vs. after	% Reduction	Interval (days)
Age						
Below median	105 (50.5)	997.0±896.2	269.2±294.2	*p*<0.01	65.2±26.1	35.0±35.1
Above median	103 (49.5)	1091.6±1119.7	395.4±360.9	*p*<0.01	57.8±22.0	50.0±71.8
Below vs. above	–	NS	*p*<0.01	–	*p*<0.01	NS
Body mass index						
Below median	104 (50.0)	1232.6±1198.2	414.2±397.0	*p*<0.01	59.3±23.1	39.2±43.4
Above median	104 (50.0)	855.1±741.2	249.2±230.4	*p*<0.01	63.8±25.6	45.7±67.6
Below vs. above	–	*p*<0.05	*p*<0.01	–	NS	NS
Creatinine						
Below median	103 (49.5)	641.2±508.0	229.3±215.3	*p*<0.01	59.6±24.4	45.8±65.8
Above median	105 (50.5)	1438.7±1210.9	432.1±395.2	*p*<0.01	63.4±24.4	39.2±46.3
Below vs. above	–	*p*<0.01	*p*<0.01	–	NS	NS
Ejection fraction						
Below median	104 (50.0)	1293.3±1190.3	359.6±377.7	*p*<0.01	67.9±22.3	37.7±36.0
Above median	104 (50.0)	794.4±717.4	303.8±283.1	*p*<0.01	55.2±24.9	47.2±71.6
Below vs. above	–	*p*<0.01	NS	–	*p*<0.01	NS

Medians: Age, 72.5 years; BMI, 23.4 kg/m²; Cr, 1.2 mg/dl; EF, 39.2%.

were equivalent (not significant). When analysed on the basis of Cr, plasma BNP levels were significantly higher in the high Cr group than in the low Cr group both before and after treatment (both *p*<0.01). Table 2 also shows the rate of reduction in plasma BNP levels between the first and second samples. The reduction rate was significantly high in the younger age group and the low EF group compared with that observed in the older age group and the high EF group, respectively. However, the reduction rates were equivalent in the high and low BMI and high and low Cr groups. No significant differences were observed in the values of the intervals between the first and second blood samplings.

The values of BNP before and after treatment were divided into five groups according to quintiles (Q1−Q5), and age, BMI, Cr, and EF before and after treatment in
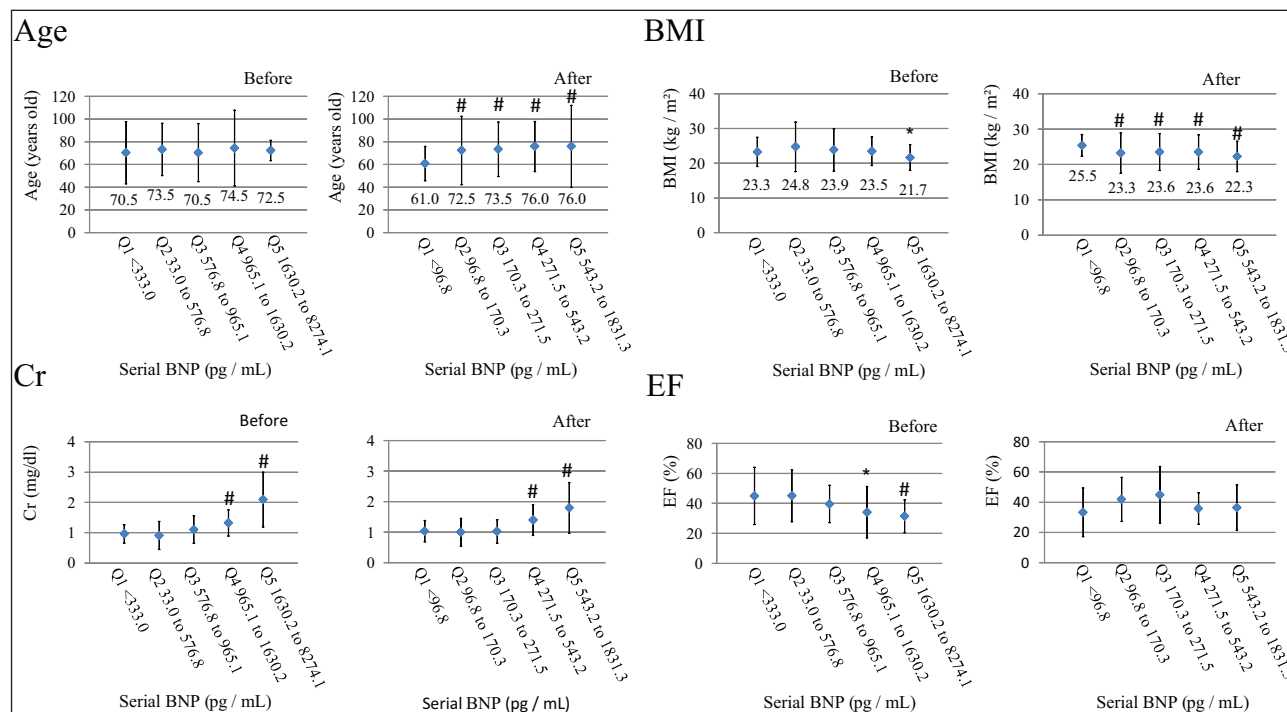
Figure 3. Changes in age, BMI, creatinine, and ejection fraction before and after treatment classified on the basis of quintiles. Significance: *$p<0.05$; #$p<0.01$.
BMI, Body mass index; BNP, B-type natriuretic peptide; Cr, creatinine; EF, ejection fraction.

group Q1 was compared to those in the other groups, from Q2 to Q5 (Figure 3). In the analysis of age, no significant differences were observed in any quintiles before treatment compared to group Q1, whereas groups Q2−Q5 showed significantly higher values after treatment. This suggests that BNP values of older patients tend to be higher after treatment than before treatment. Regarding BMI before treatment, only group Q5 showed significantly lower values than group Q1. However, BMI after treatment was significantly lower in groups Q2−Q5 compared to those observed in group Q1. Using quintiles revealed that BMI is more likely to be lower in accordance with BNP increments after treatment. Regarding the plasma Cr levels, groups Q4 and Q5 showed significantly higher levels before treatment and groups Q4 and Q5 showed significantly higher levels after treatment, which suggests that plasma BNP levels tend to be higher before and after treatment. The EF values in groups Q4 and Q5 were significantly lower than those in group Q1 before treatment. Notably, no significant differences in EF were observed in any quintiles after treatment compared to group Q1, which suggests that systolic function has no relationship with plasma BNP levels after treatment.

Clinical factors affecting log plasma BNP levels before and after treatment

Table 3 shows the results obtained from the multiple regression analysis. BMI, Cr, and EF were significantly associated with the plasma levels of BNP before treatment ($p<0.01$); however, age was not significantly associated with these plasma levels. In contrast, age, BMI, and Cr were significantly associated with the plasma levels of BNP after treatment ($p<0.01$); however, EF did not show a statistically significant contribution after treatment.

Clinical factors contributing to reduction in plasma BNP levels to <200 pg/ml after treatment

Table 4 shows the results of multiple logistic regression analyses performed to identify the clinical factors affecting plasma BNP levels after treatment (reducing the levels to <200 pg/ml). Plasma BNP levels were reduced to <200 pg/ml after treatment in 102 patients. A multiple logistic regression analysis showed that renal dysfunction and older age were negatively associated and high BMI were positively associated with plasma BNP levels <200 pg/ml. However, EF was not statistically significantly associated with BNP levels.

Kaplan−Meier curve for MACE and all-cause mortality

The plasma BNP values after treatment were divided by 200 pg/ml in Table 4. We investigated clinical

Table 3. Multiple regression analysis identifying clinical factors influencing the log plasma B-type natriuretic peptide levels before (R^2=0.258) and after (R^2=0.179) treatment.

Variable	p-value	Standard β-coefficient	β-coefficient	95% CI
Before treatment				
Age	NS	−	−	−
BMI	p<0.01	−0.170	−0.035	−0.062 to −0.009
Cr	p<0.01	0.331	0.176	0.112 to 0.239
EF	p<0.01	−0.318	−0.018	−0.025 to −0.011
After treatment				
Age	p<0.01	0.282	0.021	0.010 to 0.031
BMI	p<0.01	−0.217	−0.054	−0.086 to −0.021
Cr	p<0.01	0.257	0.163	0.086 to 0.240
EF	NS	−	−	−

BMI, body mass index; Cr, creatinine; EF, ejection fraction.

Table 4. Multiple logistic regression analysis identifying the clinical factors contributing to reductions in plasma B-type natriuretic peptide levels to <200 pg/ml after treatment.

Independent variable	p-value	β-Coefficient	Odds ratio	95% CI
Gender	NS	−	−	−
Age	<0.05	−0.026	0.974	0.950 to 0.958
BMI	<0.05	0.085	1.089	1.006 to 1.179
Cr	<0.01	−0.763	0.466	0.290 to 0.749
EF	NS	−	−	−

BMI, body mass index; Cr, creatinine; EF, ejection fraction.
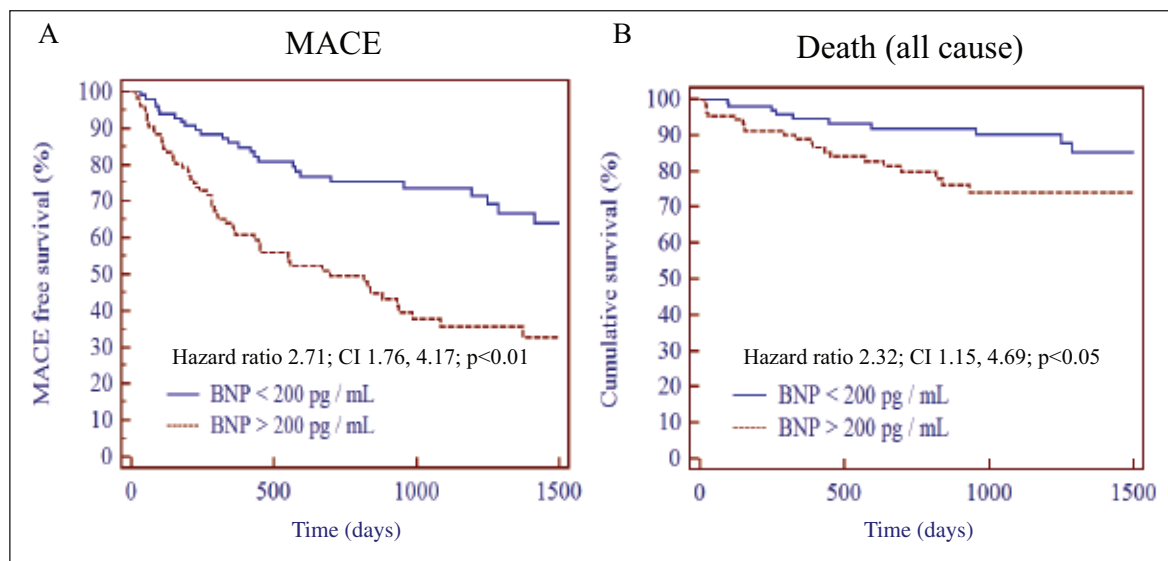
Figure 4. Major adverse cardiovascular event-free survival curves (A) and cumulative survival curves (B) for plasma BNP >200 and <200 pg/ml.
Patients with plasma BNP >200 pg/ml showed worse outcomes for MACE events and all-cause mortality. Eight patients died after admission and these patients are included in the survival curve.
BNP, B-type natriuretic peptide; MACE, major adverse cardiovascular event.

outcomes using a Kaplan−Meier curve for MACE (Figure 4A) and all-cause mortality (Figure 4B). Patients with BNP values >200 pg/ml showed worse outcomes than those with BNP values <200 pg/ml in both the MACE-free survival curve and the cumulative survival curve.

Discussion

In the present study, we investigated the clinical factors associated with decreases in plasma BNP levels and amelioration of acute heart failure. Improvements in acute heart failure are expected to differ depending on the specific characteristics of the patient, including degree of cardiac dysfunction, underlying heart disease, and the presence of complicating diseases. However, the present study identified standard contributing factors affecting changes in plasma BNP levels.[15] Serial BNP measurements are useful in evaluating acute heart failure, and we attempted to investigate improvements in acute heart failure by assessing such measurements.[9]

In terms of aging, no significant differences were observed in plasma BNP levels before treatment between older and younger age groups, suggesting that the degree of acute heart failure is not related to aging in the acute phase (Figure 2). However, the reduction rate was significantly different between the two groups and plasma BNP levels were reduced only slightly in the older age group after treatment (Figure 2). Aging was negatively associated with BNP levels <200 pg/ml after treatment (Table 4). Aging was significantly associated with plasma BNP levels after treatment only. These data suggest that aging is a key factor modulating plasma BNP levels after treatment (but not before treatment) and that older age is related to poorer prognoses.[16]

Plasma BNP levels before treatment were significantly higher in the low BMI group compared with those observed in the high BMI group. The reduction rate was similar and plasma BNP levels remained high in the low BMI group (Figure 2). BMI was significantly associated with plasma BNP levels both before and after treatment. BMI was also significantly associated with plasma BNP levels >200 pg/ml, and this result was consistent before and after treatment, which suggests that high BMIs are positively associated with BNP reduction (Table 4). This obesity paradox has also been shown in recent studies, thus suggesting that a moderately high BMI may be preferable.[17,18] However, the median BMI was only 23.4 kg/m^2 in this study, which is quite low compared with that observed in Western countries.[19,20] Therefore, the present study may only suggest that nutritional status is important for improving acute heart failure and reducing plasma BNP levels.

A recent study[21] demonstrated that the obesity paradox does not exist in patients with diabetes mellitus (DM). In that study, all-cause mortality increased in obese patients with diabetes, which suggests that it is necessary to consider the presence of DM when investigating plasma BNP levels in patients with acute heart failure.[21] We investigated the clinical outcomes in obese (above median: BMI >23.4 kg/m^2) and non-obese patients (below median: BMI <23.4 kg/m^2) with and without DM using a Kaplan−Meier curve for MACE and all-cause mortality. In the patients without DM, those who were non-obese showed worse outcomes than those who were obese in both the MACE-free survival curve (hazard ratio 0.32, 95% CI 0.18 to 0.56, *p*<0.001) and the cumulative survival curve (hazard ratio 0.21, 95% CI 0.09 to 0.51, *p*<0.05). In patients with DM, no significant differences were observed between non-obese and obese patients in outcomes in either the MACE-free survival curve or the cumulative survival curve (not significant, respectively, data not shown).

Plasma BNP levels before treatment were significantly high in the low EF group compared with those observed in the high EF group (Figure 2). However, the reduction rate was significantly higher in the group with an EF below median than in the group with an EF above median. No differences were observed in plasma BNP levels after treatment between these two groups (Figure 2). In addition, a multiple regression analysis showed that the contribution of EF to plasma BNP levels was reduced after treatment compared with that observed before treatment (Table 3). Given the fact that diastolic dysfunction is likely to affect plasma BNP levels after treatment, plasma BNP levels may correlate with diastolic dysfunction. To demonstrate this hypothesis, we evaluated echocardiographic diastolic function parameters [peak mitral inflow velocity and tissue Doppler velocities during early diastole (E and E′)] and plasma BNP levels after treatment in 30 patients who underwent echocardiographic examination in which echocardiographic E/E′ was evaluated. However, E/E′ was not measured in all patients and data for only 30 patients were measured, which was a limitation of this study. Plasma BNP levels after treatment were significantly correlated with E/E′ (*r*=0.51, *p*<0.05) (data not shown). These results suggest that intensive treatment during the acute phase can overcome increases in plasma BNP levels induced by systolic dysfunction and indicate that diastolic dysfunction is probably difficult to treat. EF was not significantly associated with plasma BNP levels >200 pg/ml after treatment, suggesting that EF is not a factor for determining prognosis (Table 4).

Elevated plasma BNP levels are associated with renal dysfunction.[22–24] In this study, plasma BNP levels were significantly reduced in the high and low Cr groups, while the reduction rate was equivalent between the two groups (Figure 2). A multiple regression analysis showed that plasma BNP levels both before and after treatment were associated with renal dysfunction (Table 3). In addition, renal dysfunction was positively associated with levels >200 pg/ml after treatment (Table 4). These results suggest that renal dysfunction is a factor acting against amelioration of heart failure during both acute and recovery phases.

In conclusion, the contributions of clinical factors acting against amelioration of heart failure vary before and after treatment. The most important finding of this study is that plasma BNP levels are associated with systolic dysfunction in the acute phase but not after treatment. This suggests that

diastolic dysfunction is hardly improved, even with intensive treatment. Regarding plasma BNP levels, an older age, very low BMI, and the presence of renal dysfunction eventually act to prevent an amelioration of acute heart failure. Systolic dysfunction does not have a negative influence on any amelioration of acute heart failure.

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Conflict of interest

No authors have any conflicts of interests to disclose.

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