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The response of NT-proBNP to intensified medication in advanced chronic heart failure☆

Hiroki Nakano [a], Koichi Fuse [a], Minoru Takahashi [a], Sho Yuasa [a], Tomoyasu Koshikawa [a], Masahito Sato [a], Masaaki Okabe [a], Akira Yamashina [b], Yoshifusa Aizawa [c,d,*]

[a] Tachikawa General Hospital, Cardiology, Nagaoka City, Niigata, Japan
[b] Tokyo Medical University, Internal Medicine, Tokyo, Japan
[c] Tachikawa Medical Center, Research and Development, Nagaoka, Niigata, Japan
[d] Niigata University, Niigata, Japan

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ABSTRACT

Background: The clinical significance of excessively high serum NT-proBNP is poorly understood in chronic heart failure (HF).
Methods: One-hundred eighteen patients with advanced chronic HF (NYHA functional class III or IV) were admitted; of these patients, 42.4% exhibited NT-proBNP levels >10,000 pg/ml. The patients were divided into three groups as follows: ≥400 and <10,000 pg/ml, group I (n = 68); ≥10,000 and <20,000 pg/ml, group II (n = 28); and ≥20,000 pg/ml, group III (n = 22). The determinants of elevated NT-proBNP levels and responsiveness to HF medications were compared among these groups. A subgroup of HF patients with normal serum creatinine was analyzed separately.
Results: Overall, cardiac, renal and laboratory parameters (serum creatinine, potassium and uric acid, positively; and eGFR and hemoglobin, negatively) correlated with serum NT-proBNP levels. In patients with normal serum creatinine, left ventricular ejection fraction, serum potassium and hemoglobin correlated with serum NT-proBNP levels. In-hospital mortality was higher in patients with the highest NT-proBNP levels. After successful HF treatment, the patients in each group lost body weight and improved to NYHA class I or II, and NT-proBNP levels were halved, irrespective of their baseline levels. Excessively high NT-proBNP levels were related to cardiac, renal and laboratory abnormalities; therefore, the role and underlying mechanism of high NT-proBNP levels must be studied further.
Conclusion: Excessively high NT-proBNP levels in HF patients correlated with cardiac, renal and laboratory parameters. After successful HF treatment, NT-proBNP levels were halved, irrespective of their baseline levels. The precise role and underlying mechanism of NT-proBNP warrant further study.

1. Introduction

The prevalence of chronic heart failure (HF) is increasing in many developed countries. Both bioactive brain-type natriuretic peptide (BNP) and an inactive marker molecule (NT-proBNP), which is derived from the BNP precursor [1–4] have been used for the diagnosis and pharmacological management of HF [5,6].

BNP clearance occurs in the kidney, liver, and vascular endothelium through clearance receptor and neutral endopeptidase [7], whereas NT-proBNP is believed to be cleared solely in the kidney through unknown mechanism [1,8].

Because NT-proBNP has some advantages over BNP, including higher circulating levels and superior stability, and only a small amount of serum is required for its measurement [9–11], we used NT-proBNP for the diagnosis and evaluation of HF severity in this study.

However, it is not uncommon to encounter patients with advanced HF who present with excessively high levels of NT-proBNP, i.e., >10,000–30,000 pg/ml. In such patients, the determinants of cardiac peptide levels and their responsiveness to intensified HF therapy are poorly understood.

2. Patients and methods

Between April 2012 and March 2014, 118 adults were admitted to our hospital for decompensated chronic HF. They had been treated by cardiologists at the outpatient clinic, according to the guideline for HF treatment [12,13]. At the time of admission, all patients exhibited

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* Corresponding author at: Tachikawa Medical Center, Research and Development, Nagaoka City, Niigata 940-8621, Japan.
E-mail address: aizaways@med.niigata-u.ac.jp (Y. Aizawa).

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symptoms characteristic of NYHA functional class III or IV, and intensified HF treatment was attempted.

The exclusion criteria were as follows: the performance or the planning of an urgent invasive or surgical intervention during admission, severe chronic obstructive pulmonary disease or pulmonary embolism less than 3 months prior to admission, and pulmonary hypertension not caused by left ventricular systolic dysfunction. Patients with mitral regurgitation of more than moderate severity secondary to ischemic or non-ischemic cardiomyopathy, patients with valvular heart disease and patients on chronic hemodialysis or peritoneal dialysis were also excluded.

2.1. Management during hospitalization

After physical examination of patients, a blood sample was drawn to collect laboratory data, including an NT-proBNP level; lab test were measured (using the ECLIA method) after admission and before discharge. An ECG, chest X-ray and echocardiogram were performed. The estimated glomerular filtration rate (eGFR) was calculated using a revised equation for Japanese people, and chronic kidney disease (CKD) was defined as an eGFR <60 ml/min/1.73 m^2 [14].

After admission, patients were maintained on bed-rest. Both fluid and salt intake were controlled, and diuresis was facilitated via either loop diuretics alone or in combination with ANP [15] until symptoms of congestion resolved. HF medication dosages were increased or decreased when necessary, and additional medications were utilized for specific patients as tolerated. Patients suffering from tachycardic atrial fibrillation received either verapamil or a beta-blocker to maintain a ventricular rate of less than 100 beats per minute. The clinical endpoints were the resolution of peripheral edema and pulmonary congestion, as well as other symptoms, and patients were discharged in NYHA class I or II.

2.2. Data analysis

Baseline patient clinical data were analyzed and the correlations between laboratory parameters and NT-proBNP levels were analyzed. The patients were then divided into three groups according to their basal NT-proBNP levels as follows: group I, with an NT-proBNP level ≥400 and <10,000 pg/ml; group II, with an NT-proBNP level ≥10,000 and <20,000 pg/ml; and group III, with an NT-proBNP ≥20,000 pg/ml. Baseline patient clinical data were compared among the three groups, and the correlations between laboratory data and NT-proBNP levels were analyzed. Underlying heart diseases, comorbidities and medications were also compared among the subgroups. To minimize the effect of renal dysfunction on cardiac peptide levels, a similar analysis was performed in patients with serum creatinine levels <0.1 mg/dl.

The post-hospital courses of the three groups were compared to evaluate their outcomes after discharge. Finally, changes in body weight, NYHA functional class, and serum NT-proBNP levels as well as signs and symptoms of HF, were compared among the three groups, for the patients who remained alive and discharged.

2.3. Statistical analysis

Continuous data are presented as the means ± standard deviations (SD), and the categorical variables are expressed as either absolute numbers or percentages. Statistical comparisons between groups were made using either the *t*-test or ANOVA for continuous variables or Pearson's chi-squared test for categorical variables. JMP software (Statistical Discovery Software, version 5.0.1 J, SAS Institute, Cary, NC, USA) was used to perform the statistical analysis. A two-sided test with $P < 0.05$ was considered statistically significant.

This retrospective case study was conducted according to the guidelines of clinical research in Japan and was approved by the Institutional Review Board of Tachikawa Medical Center.

3. Results

3.1. Clinical features on admission

All patients exhibited symptoms characteristic of NYHA functional classes III-IV upon admission. These clinical characteristics are shown in Table 1. The majority of patients (>70%) were male. Sixty-eight patients belonged to group I; 28, to group II; and 20, to group III (Table 1).

The mean age of group I was younger than that of the other two groups. The number of previous hospitalizations for HF was higher among the patients in group II than group I: 2.7 ± 1.8 vs. 1.7 ± 1.3 hospitalization ($P = 0.082$). The prevalence of pleural effusions was lower in group I than in the other two groups. The left ventricle was more dilated as NT-proBNP increased, and ejection fraction was significantly reduced in groups II and III compared with group I.

There were no significant differences in the prevalence of underlying heart disease and comorbidities, with the exception of valvular heart diseases, which was most prevalent in group III. CKD and dyslipidemia were more frequent in groups II and III than in group I. Otherwise, there were no significant differences in comorbidities or medications prior to hospitalization (Table 1).

As NT-proBNP increased, serum potassium, creatinine and uric acid increased, and eGFR and hemoglobin (Hb) decreased. AST and white blood cells (WBC) levels were higher in group III than group I (Table 2).

3.2. Correlation between laboratory parameters and NT-proBNP

Overall, significant correlations were observed between age, serum creatinine, ejection fraction, diastolic left ventricular diameter, Hb, serum potassium, uric acid and WBC and NT-proBNP (Fig. 1, Table 3). Among the 3 subgroups, significant correlations were observed in these parameters: between NT-proBNP levels and serum creatinine in group I, NT-proBNP and WBC in group II and NT-proBNP and serum creatinine in group III.

The relationship between NT-proBNP levels and other laboratory parameters was evaluated separately in 50 patients with preserved renal function. In this subgroup, all patients had a normal serum creatinine:

Table 1
Patients' clinical characteristics.

	Group I (n = 68)	Group II (n = 28)	Group III (n = 22)	I vs. II/I vs. III
Age (yrs.)	76.7 ± 11.7	73.9 ± 25.1	82.9 ± 8.3	0.06/0.024
Male, n (%)	48 (72.7)	20 (71.4)	16 (72.7)	0.934/0.395
No. of admissions	1.7 ± 1.3	2.7 ± 1.8	1.7 ± 1.1	0.031/0.829
Ejection fraction (%)	47.5 ± 15.8	38.9 ± 14.6	39.4 ± 16.6	0.015/0.048
LVDD (mm)	52.5 ± 10.0	53.6 ± 7.6	56.0 ± 13.2	0.616/0.208
Pleural effusion	39 (57.4%)	20(71.4)	20(100.0)	0.040/0.030
UDH, n (%)				
Ischemic HD	27(39.7)	11 (39.3)	9 (40.9)	0.970/0.673
Valvular HD	42(61.8)	17(60.7)	18 (81.8)	1.000/0.017
Non-ischemic CM	10 (14.7)	5(17.9)	7 (31.8)	0.702/0.448
Hypertension	53(77.9)	24 (85.7)	13 (59.1)	0.526/0.938
Diabetes mellitus	21(30.9)	7(25.0)	6(27.3)	0.561/0.940
Dyslipidemia	18 (26.5)	7 (25.0)	7 (31.8)	0.561/0.744
CKD	46(67.6)	25(89.3)	20(100.0)	0.020/<0.001
AF/FL	39 (57.4)	12 (42.9)	10 (45.5)	0.198/0.562
VT	3 (4.4)	0	1 (4.5)	1.000/0.913
Miscellaneous	3 (4.4)	2(7.1)	3 (13.6)	0.595/0.129
Medication, n (%)				
ACEI/ARB	39 (57.4)	12 (42.9)	12 (54.5)	0.255/0.833
Beta-blockers	16 (23.5)	11 (39.3)	9 (40.9)	0.125/0.069
Diuretics	60 (88.2)	28(100.0)	25 (100.0)	0.058/0.108
Anti-aldosterone	16 (23.5)	8(14.3)	7 (31.8)	0.607/0.315
CCB	34(50.0)	11(39.3)	9(40.9)	0.276/0.610
Digoxin	13 (19.1)	5 (17.9)	4 (18.2)	0.885/0.930
AA	34 (50.0)	9 (32.1)	7 (31.8)	0.082/0.192

AA: antiarrhythmic agent. AF/FL: atrial fibrillation/flutter. CCBs: calcium channel blockers. CKD: chronic renal disease. CM: cardiomyopathy. HD: heart disease. LVDD: Left ventricular diastolic dimension. VT: ventricular tachycardia. UDH: underlying heart disease.

Table 2
Laboratory findings among the three patient groups.

	Group I (n = 68)	Group II (n = 28)	Group III (n = 22)	P value I vs. II/I vs. III
Na (mEq/l)	140.0 ± 4.0	139.2 ± 3.8	139.1 ± 4.1	0.273/0.453
K (mEq/l)	4.2 ± 0.6	4.4 ± 0.5	4.8 ± 0.8	0.176/<0.001
Cl (mEq/l)	104.2 ± 4.7	104.7 ± 5.4	105.5 ± 4.7	0.929/0.254
WBC (μl)	7176 ± 3807	7617 ± 3134	10,337 ± 7090	0.589/0.009
CRP (mg/dl)	2.26 ± 4.58	2.04 ± 2.06	3.25 ± 3.21	0.818/0.361
Hb (g/dl)	12.1 ± 2.6	10.7 ± 2.0	9.8 ± 2.4	0.008/<0.001
s-Cre (mg/dl)	1.22 ± 0.58	1.61 ± 0.96	2.20 ± 1.82	0.018/<0.001
eGFR	38.5 ± 26.5	45.5 ± 30.4	28.7 ± 19.8	0.544/<0.001
AST (U/l)	93.0 ± 452[a]	44.0 ± 23.4	108.0 ± 203.0	0.348/0.007
ALT (U/l)	57.6 ± 224.2	35.1 ± 26.0	62.0 ± 105.8	0.599/0.931
T-Bil (mg/dl)	0.86 ± 0.46	0.82 ± 0.43	0.9 ± 0.6	0.776/0.984
TP (g/dl)	6.3 ± 0.8	6.37 ± 0.60	6.53 ± 0.78	0.836/0.351
UA (mg/dl)	6.7 ± 1.8	7.2 ± 2.0	9.3 ± 3.2	0.298/<0.001

ALT: alanine aminotransferase. AST: aspartate aminotransferase. CRP: C-reactive protein. Hb: hemoglobin. eGFR: ml/min/1.73 m^2. s-Cre: serum creatinine. T-Bil: total bilirubin. TP: total protein. UA: serum uric acid.
[a] One patient had high AST level: 3700 U/l.

Table 3
Correlations between laboratory data and serum NT-proBNP levels.

	All	Group I	Group II	Group III
Age	–	–	–	–
S-CR	r = 0.24 (0.009)	r = 0.39 (0.001)	–	r = 0.55 (0.009)
eGFR	r = 0.21 (0.025)	r = 0.28 (0.023)	–	–
LVDD	r = 0.19 (0.040)	–	–	–
EF	r = 0.33 (<0.001)	–	–	–
Hb	r = 0.28 (0.003)	–	–	–
K	r = 0.28 (0.003)	–	–	–
UA	r = 0.40 (<0.001)	–	–	–
WBC	r = 0.26 (0.005)	r = 0.26 (0.035)	r = 0.40 (0.035)	–
AST	r = 0.26 (0.005)	–	–	–

Abbreviations are the same in Tables 1 and 2.

<1.0 mg/dl, 0.79 ± 0.12 mg/dl. The mean age was 78.2 ± 12.7 years, and the NT-proBNP levels was 9032 ± 9490 pg/ml with a range from 789 pg/ml to 34,739 pg/ml. The ejection fraction significantly correlated with NT-proBNP (r = 0.32, P = 0.002), whereas the left ventricular dimension did not (r = 0.03, P = 0.825). Significant correlations were found between NT-proBNP and serum potassium (r = 0.50, P < 0.001) and NT-proBNP and hemoglobin (r = 0.41, P = 0.003).

3.3. Courses after hospitalization

In addition to bed-rest and restricted salt intake, patients received loop diuretics, both with and without intravenous atrial natriuretic peptide. Either an ARB or ACEI was initiated in 8 patients (4, 1 and 3 patients in groups I, II and III, respectively), and dosages were intensified in 7 patients (4, 1 and 2 patients in groups I, II and III, respectively). In 9 patients (3 patients in each group), the dose of either an ARB or an ACEI was reduced because of either low blood pressure or increased serum potassium. Beta blocker treatments were initiated in 12 patients (10, 1 and 1 patients in groups I, II and III), and the dosages were increased in 2 patients in group II and decreased in 4 patients and 1 patient in groups I and III, respectively. Aldosterone antagonist treatments were initiated in 11 patients (7, 3 and 1 patient in groups I, II and III), and dosages were decreased in 12 patients (5, 3 and 4 patients in groups I, II and III) due to increased serum potassium levels or renal dysfunction.

Another diuretic was administered to 18 patients (13, 2 and 3 patients in groups I, II and III); diuretic dosages were increased in 20 patients (14, 5 and 1 patients). Loop diuretic dosages were decreased in 18 patients (11, 5 and 2 patents in groups I, II and III) to prevent hyponatremia. Abnormal CRP levels and WBCs normalized both with and without the use of antibiotics, and AST and ALT levels also normalized within a week without specific treatment.

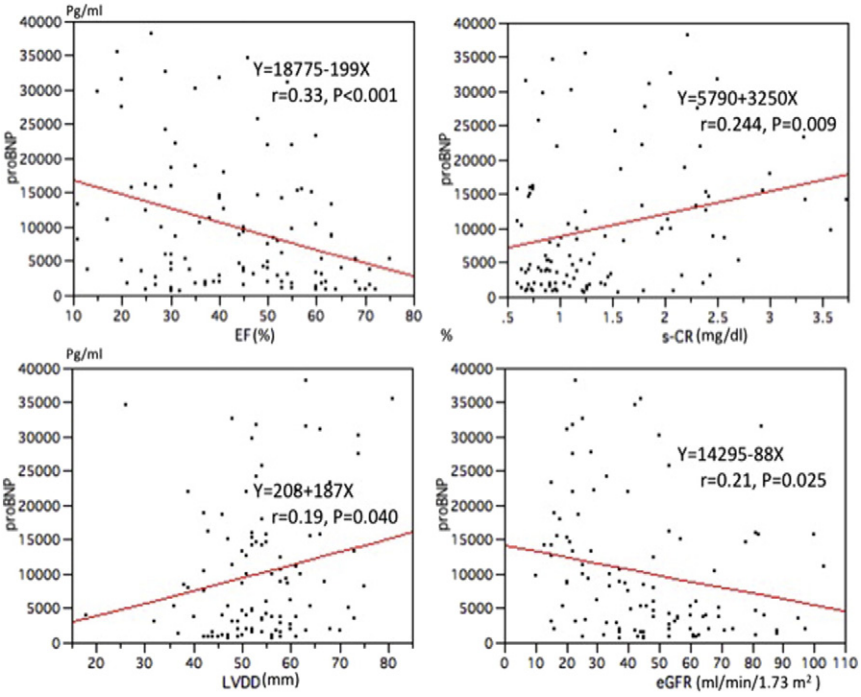

Fig. 1. The correlations between NT-pro BNP levels and cardiac or renal parameters. Serum NT-proBNP levels were weakly but significantly correlated with ejection fraction (EF), left ventricular dimension (LVDD), serum creatinine (s-CR) and estimated glomerular filtration rate (e-GFR). All patients were within NYHA functional class III or IV and exhibited evidence of congestion. Correlations between age and laboratory parameters with NT-proBNP are summarized in Table 3.

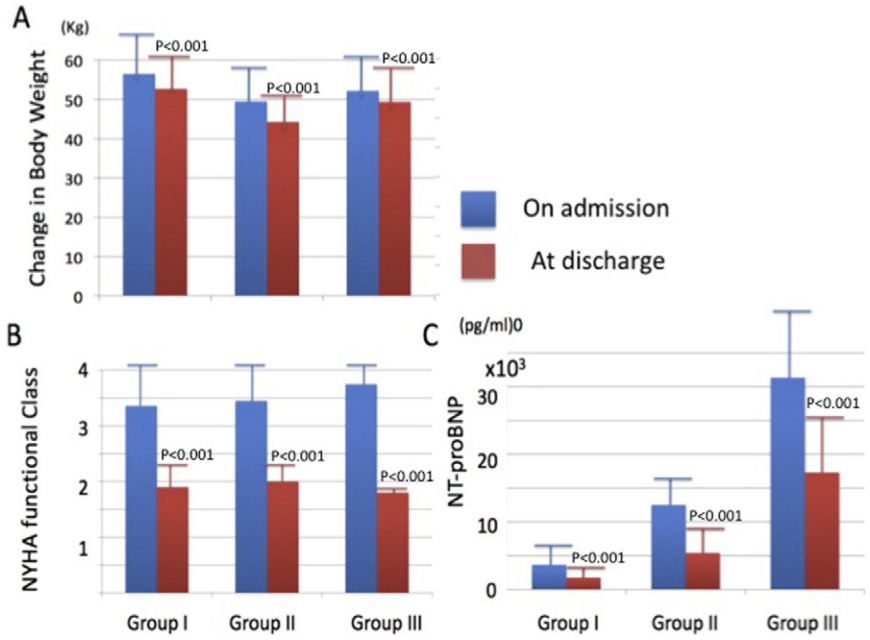

Fig. 2. Changes in body weight, NYHA functional class and NT-proBNP. Upon discharge, patients in each group lost body weight from 4.2–4.6 kg ($P < 0.001$) of body weight. The NYHA functional class was reduced to less than II ($P < 0.001$), and the NT-proBNP levels decreased to half of their baseline ($P < 0.001$). Means with one SD are shown at the time of admission and discharge.

3.4. Outcomes and NT-proBNP

Of the 118 patients included in this study, 11 patients died during their hospitalizations from HF, including 3 patients (4.4%) in group I, 1 patient (3.6%) in group II and 7 patients (35%) in group III; the mortality rate was significantly higher in group III than group 1 ($P < 0.001$) or group II ($P = 0.04$). Mean age and NT-proBNP levels were higher among the patients who died compared with those who were discharged alive as follows: 88.4 ± 5.7 years vs. 77.8 ± 10.9 years ($P < 0.001$) and 22,186 ± 11,977 pg/ml vs. 9602 ± 11,537 pg/ml ($P < 0.001$), respectively.

The 107 patients discharged alive were in NYHA class II or I. The hospitalization durations were 27 ± 18 days, 29 ± 19 days and 43 ± 45 days in groups I, II and III, respectively, and the duration was significantly longer in group III than group I ($P = 0.0185$). Patients lost an average of 4.6 ± 3.6 kg, 4.3 ± 3.5 kg and 4.2 ± 3.2 kg of body weight in groups I, II and III, respectively (no significant difference) by the time of discharge. NT-proBNP levels were reduced by 46.9 ± 36.1%, 56.5 ± 29.4% and 43.2 ± 38.1%, in groups I, II and III, respectively; the differences among the three groups were not significant ($P = 0.3988$–0.7520, Fig. 2).

During the two year follow up after discharge, 12 patients died, including 5 (7.7%), 4 (14.8%) and 3 (23.1%) patients in groups I, II and III, respectively, and 32 patients were readmitted, including 19 (29.2%), 8 (29.6%) and 5 (38.5%) patients in groups I, II and III, respectively. There were no significant differences in the mortality or readmission rates among the three groups after discharge.

4. Discussion

NT-proBNP levels > 10,000 pg/ml were found in 42.4% of ambulatory HF patients who were admitted to our hospital in NYHA class III or IV. As NT-proBNP levels increased, the left ventricle became more dilated, and serum potassium, creatinine, WBC, and uric acid became elevated, whereas eGFR and hemoglobin decreased. Although the association was weak, NT-proBNP levels significantly correlated with these parameters. In patients with normal renal function, NT-proBNP levels correlated with ejection fraction.

Patients with higher NT-proBNP levels upon admission were at higher risk for in-hospital mortality. The patients discharged alive were all in NYHA functional class I or II, and their signs and symptoms of congestion has resolved. At discharge, NT-proBNP levels had decreased to a half of their baseline values. For patients with excessively high NT-proBNP levels, the cardiac peptide may be a marker of the severity of HF; treating HF until the initial NT-proBNP level is halved could be an endpoint of intensified HF therapy. However, the determinants of serum NT-proBNP in advanced HF patients are still not fully understood.

4.1. NT-proBNP in HF

NT-proBNP may be the preferred laboratory parameter for some clinicians for guiding HF treatment [10,16–22]. In the majority of previous studies [10,16–21], baseline NT-proBNP levels ranged from 3000 to 5000 pg/ml, and the target cardiac peptide level for treatment was set at either a predetermined target or the lowest level [10,13,16–21]. However, there are many patients who exhibit very high NT-proBNP levels; approximately 40% of the patients enrolled in this study exhibited NT-proBNP levels > 10,000 pg/ml. In patients who present with excessively high serum NT-proBNP, it would be unrealistic to expect their levels to normalize. As a target of intensified HF therapy, a reduction in NT-proBNP to half of its baseline level seems realistic, irrespective of the baseline level (Fig. 2). However, other factors may also affect or modulate serum NT-proBNP levels in advanced HF patients. The determinants and dynamics of NT-proBNP during HF treatment require further study.

4.2. Changes in NT-proBNP during HF treatment

The major determinants of serum NT-proBNP levels are the release of the peptide from the heart and the clearance and/or degradation of the peptide by the kidney. In acute HF, the heart is exposed to increased wall stress and the release of proBNP is increased; it has been demonstrated that NT-proBNP levels correlate well with hemodynamic alterations [23].

In the present study, left ventricular ejection fraction decreased as NT-proBNP increased (Table 1). A significant correlation between

serum NT-proBNP levels and left ventricular ejection fraction supports the conclusion that the latter is a determinant of cardiac peptide levels (Fig. 1, Table 3). When the effect of renal dysfunction was minimized by analyzing only patients with normal renal function (serum creatinine < 0.1 mg/dl), a significant correlation was observed between left ventricular ejection fraction and NT-proBNP. A relatively weak correlation, however, may suggest the presence of other determinants of excessively high NT-proBNP levels.

NT-proBNP is eliminated from the kidneys by clearance and/or degradation, but the precise mechanism underlying this phenomenon has not yet been clarified [7,8,24–27]. As serum creatinine increased (and eGFR decreased), NT-proBNP increased, and a significant correlation was observed between serum creatinine and NT-proBNP (Fig. 1, Tables 2 and 3).

By the time of discharge, all patients were free from symptoms and signs of congestive HF and had lost an average of 4.2 to 4.6 kg of body weight. The reduction in body weight represented the removal of excess body fluid. When decompensated HF improved, serum NT-proBNP levels decreased to approximately half of their baseline levels, irrespective of these baseline levels.

It is likely that the fall of serum NT-proBNP was induced by the major two mechanisms: a reduction in the release of the cardiac peptide from heart and augmented clearance or degradation by the kidney, but other factors must be involved to account for the excessively high levels of the peptide observed in this study and elsewhere.

Several parameters correlated with NT-proBNP levels: serum potassium, uric acid, hemoglobin, AST and WBC. Some of these parameters reflect impaired renal function, whereas others may affect NT-proBNP dynamics in an unknown way. After the intensification of HF medication therapy during the hospitalization, large changes in NT-proBNP levels were observed in each patient in conjunction with resolution of HF signs and symptoms, even among the patients with excessively high baseline levels of the peptide.

4.3. Limitations

This study treated a relatively small number of patients suffering from advanced HF secondary to heterogeneous underlying heart diseases. Most patients had multiple comorbidities. The study did not include pressure readings from the ventricles or the pulmonary artery, and NT-proBNP or its degraded products were not measured in the urine. The relationship between HF improvement and NT-ProBNP levels warrants further study in advanced HF patients. However, a similar decrease in NT-proBNP levels occurred irrespective of baseline values after the successful intensification of HF therapy, and these findings are not likely to be coincidental phenomena.

5. Conclusion

In our study, patients with advanced HF (NYHA class III or IV) exhibited excessively high levels of NT-proBNP on admission. Cardiac, renal and some laboratory parameters correlated with the NT-proBNP levels. Irrespective of their baseline values, NT-pro-BNP levels were halved by intensified HF treatment, and the signs and symptoms of HF were successfully improved to NYHA II or I. The determinants and the mechanisms regulating NT-proBNP dynamics warrant further study.

6. Clinical perspectives

Excessively high NT-proBNP levels of 10,000 pg/ml or higher can be observed in advanced heart failure patients. In our study, patients were admitted in NYHA class III or IV HF. In our sample, a significant but weak correlation was observed between cardiac or renal function and other laboratory parameters and NT-proBNP. In patients with preserved renal function (serum creatinine < 1.0 mg/dl), NT-proBNP levels significantly correlated with ejection fraction, but not with left ventricular dimension. The determinants and the mechanisms underlying the dynamic response of NT-proBNP must be examined in advanced HF patients. Higher NT-proBNP levels were associated with increased in-hospital mortality. When patients improved to NYHA functional class I or II with intensified medication therapy, the NT-proBNP levels decreased to a half of their baseline levels, irrespective of the initial levels. Such a fall in NT-proBNP could be a marker of a therapeutic endpoint in the treatment of advanced heart failure.

Conflicts of interest

None.

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