

Stability of NT-ProBNP in Patients With Systolic Heart Failure

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Natriuretic peptides are extremely useful in the diagnosis and prognosis of patients with heart failure. However, it is not clear whether their values are stable. We carried out a prospective study of 30 consecutive ambulatory patients (mean age, 62.6 [12.2] years) with stable systolic heart failure, as determined by the 6-minute walk test, who were in New York Heart Association class II or III and who had a left ventricular ejection fraction <30% (mean ejection fraction, 24.2% [6.68%]). At baseline, the mean N-terminal pro-brain natriuretic peptide (NT-proBNP) level and the mean distance walked in 6 minutes were 2237.3 pg/mL and 348.26 m, respectively. At 3-month follow-up, the corresponding values were 2096.2 pg/mL and 372.05 m, respectively. No significant difference was observed in NT-proBNP level or in distance walked in 6 minutes between baseline and 3 months ($P=.8$). Overall, there was a good correlation ($r=0.94$; $P<.001$) between the plasma NT-proBNP level at baseline and at 3 months in patients with stable chronic heart failure due to systolic dysfunction in New York Heart Association class II or III.

Key words: Heart failure. Natriuretic peptides. Prognosis.

Estabilidad de NT-proBNP en pacientes con insuficiencia cardiaca sistólica

Los péptidos natriuréticos tienen un alto valor diagnóstico y pronóstico en pacientes con insuficiencia cardiaca, pero desconocemos la estabilidad de sus valores. Determinamos en 2 visitas ambulatorias los valores de N terminal pro-BNP (NT-proBNP) de 30 pacientes consecutivos con insuficiencia cardiaca estable [New York Heart Association (NYHA) II-III] (test 6 min) por disfunción sistólica [función ventricular izquierda deprimida (FEVI) < 30%] separadas entre sí 3 meses. Tenían una edad media de 62,6 ± 12,2 años y una fracción de eyección del 24,2 ± 6,68%. No encontramos diferencias significativas entre los valores basales del NT-proBNP como test de los 6 min (2.237,3 pg/ml y 348,26 m) y a los 3 meses (2.096,2 pg/ml y 372,05 m). El coeficiente de correlación intraclass entre los valores basales y a los 3 meses de NT-proBNP fue de 0,94 ($p < 0,001$). Existe una buena correlación entre los valores basales y a los 3 meses de las concentraciones plasmáticas de NT-proBNP en pacientes con insuficiencia cardiaca crónica estable (NYHA II-III) por disfunción sistólica.

Palabras clave: Insuficiencia cardiaca. Péptidos natriuréticos. Pronóstico.

INTRODUCTION

Natriuretic peptides, which are mainly secreted in the heart in response to specific stimuli such as pressure and volume overload, display a high diagnostic and prognostic value in patients with heart failure,¹ and they have even been suggested to act as a useful guide for

treatment of patients with heart failure requiring resynchronization.² Furthermore, there is a positive correlation between concentrations of natriuretic peptides and various endothelins, and a negative correlation with left ventricular ejection fraction.³

Various clinical conditions and demographic characteristics can affect circulating levels of B-type natriuretic peptide (BNP) and its N-terminal peptide (NT-proBNP). Women and the elderly have levels up to 3 times higher than those seen in men or young individuals, obesity is associated with lower concentrations,⁴ and various drugs (angiotensin receptor inhibitors, diuretics, and digoxin)⁵ and concomitant diseases such as thyroid diseases, renal

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failure,⁶ atrial fibrillation,⁷ and hypertension⁸ can affect levels of the peptides. Little information is available regarding the stability of NT-proBNP measurements during follow-up in patients with chronic symptomatic heart failure of any etiology. The aim of the present study was to assess the reproducibility of plasma concentrations of NT-proBNP in stable patients with heart failure caused by systolic dysfunction.

METHODS

A total of 30 individuals treated as outpatients for stable symptomatic heart failure (New York Heart Association class II-II) with an ejection fraction of less than 30% (assessed by echocardiography at enrollment) were consecutively enrolled in the study. None of the patients had been admitted to hospital or had their treatment altered in the previous 6 months. Patients were excluded from the study if they had kidney failure (defined as a plasma creatinine concentration of greater than 2 mg/dL), angina, severe bronchial disease, peripheral artery disease, or musculoskeletal disease. At the time of enrollment, a patient history was taken and a complete physical examination was performed, along with a basic laboratory workup and analysis of plasma concentrations of NT-proBNP, and finally, a 6-minute walk test. The same procedures were performed at 3-month follow-up. Patients were excluded from the study if they displayed clinical instability, which was defined as hospital admission due to cardiovascular causes, changes in cardiovascular medication, such as the addition of new drugs or changes in the dose of drugs prescribed previously (particularly diuretics), or changes in functional status. Four patients were excluded on that basis. The local ethics committee approved the study and all patients gave written informed consent to their inclusion.

Measurement of Plasma Concentrations of NT-proBNP

Blood samples were collected in EDTA tubes and centrifuged at 3000 rpm for 10 min. Plasma was then stored in aliquots at -70°C prior to analysis. NT-proBNP concentration was analyzed with a chemiluminescence enzyme-linked immunosorbent assay (Roche Diagnostics) on a 2010 analyzer. The physicians involved in the study were unaware of the values obtained for NT-proBNP concentration.

Statistical Analysis

Data are shown as means (SD). Differences between groups were analyzed using the Student *t* test for paired samples. Univariate analysis was performed using standard statistical methods. The extent of

TABLE 1. Patient Characteristics*

Demographic Data	Values
Age, y	62.6 (12.25)
Male sex	26 (86.7%)
NYHA class (II/III)	20 (66.7%)/10 (33.3%)
Etiology (HF/DCM)	22 (73.3%)/8 (26.7%)
LVEF, %	24.2 (6.68)
Hypertension	20 (66.7%)
Diabetes mellitus	10 (33.3%)
Sodium, mmol/L	139 (1.9)
Potassium, mmol/L	4.6 (0.45)
Creatinine, mg/dL	1.31 (0.48)
Medication, %	
ACE inhibitors	83.4
Angiotensin II receptor antagonists	13.3
Beta-blockers	76.7
Digoxin	13.3
Diuretics	90

*NYHA indicates New York Heart Association; HF, heart failure; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; ACE, angiotensin converting enzyme.

Data are shown as mean \pm SD or number (%), unless otherwise indicated.

TABLE 2. NT-proBNP Concentration and 6-Minute Test Results at Baseline and 3-Month Follow-Up*

Measurement	Baseline	3 Months	Intraclass Correlation Coefficient	<i>P</i>
NT-proBNP, pg/mL	2237.3	2096.2	0.94	<.001
6-minute test, m	348.26	372.05	0.79	<.001

*NT-proBNP indicates the N-terminal peptide of pro-B-type natriuretic peptide.

agreement between the two measurements was assessed with the intraclass correlation coefficient and the Bland-Altman test. Statistical significance was set at $P<.05$. Analyses were performed using the statistical package SPSS 12.0.

RESULTS

The baseline characteristics of the patients are shown in Table 1. The most common cause of heart failure was ischemia (73.3%) and patients were treated according to current guidelines; 20 patients were in functional class II, and when compared with the 10 patients in functional class III, they were younger (mean age of 58 vs 71 years), walked further in the 6-minute test (396 m vs 251 m), and had lower plasma concentrations of NT-proBNP (1257 pg/mL vs 4197 pg/mL) ($P<.001$). No significant differences were seen in terms of clinical status during the 3 months of the study. No statistically significant differences were observed between the mean results at baseline and 3-month follow-up for the concentration of NT-proBNP or the distance walked in the 6-minute test (Table 2). A strong correlation was

observed between the results for the two 6-minute tests ($r=0.79$, $P<.001$). A statistically significant correlation was seen between the 2 concentrations obtained for NT-proBNP (2237.3 ± 2426.34 pg/mL in the initial sample and 2096.2 ± 2004.22 pg/mL in the final sample; intraclass correlation coefficient, 0.94; $P<.001$) (Table 2). Bland-Altman analysis revealed a good agreement between the two measurements of NT-proBNP concentration (Figure). The largest variations in NT-proBNP concentration were seen in patients with a higher functional class, who had higher average concentrations of NT-proBNP.

DISCUSSION

BNP and its N-terminal fragment NT-proBNP are valuable for the diagnosis of left ventricular dysfunction and heart failure due their high negative predictive value⁹ and also provide prognostic information in heart failure, since the concentrations of the peptides are correlated with the severity of the disease.¹⁰ Serial measurements could be of use to follow the response to medical treatment and the clinical progress of patients.¹¹ Given the role of these peptides in the assessment of clinical progress, it is crucial to determine the intraindividual and interindividual biologic variation in the plasma concentration.¹²

Some studies have assessed the biologic variation of NT-proBNP and BNP. Melzi d'Eril et al¹³ analyzed the biologic variability of NT-proBNP in 16 healthy subjects; Wu et al¹⁴ demonstrated substantial variations in the concentrations of BNP and NTproBNP in patients with stable heart failure; and McNairy et al¹⁵ showed that when measured before and after an exercise program using an exercise bicycle, the changes in plasma concentrations of BNP were greater in healthy subjects (55%) than in patients with heart failure. Substantial variations in the concentrations of natriuretic peptides have recently been reported in stable patients with heart failure.¹⁶ However, in a study of 98 patients with heart failure, Lee et al¹⁷ found that the concentrations of BNP varied according to the patient's clinical status.

The results of our study show a good correlation between the mean concentrations of NT-proBNP ($r=0.94$, $P<.001$) in a group of stable patients (shown objectively by the strong correlation between the results of the 6-minute walk test at the beginning and end of the study) with congestive heart failure caused by systolic dysfunction. This correlation shows a higher variability (Bland-Altman test) in patients with higher concentrations of NT-proBNP, corresponding to those patients with a worse functional class.

One limitation of this study is the small number of patients included. We do not know what influence concomitant medication may have or the possible longer term variability. The 6-minute walking test was

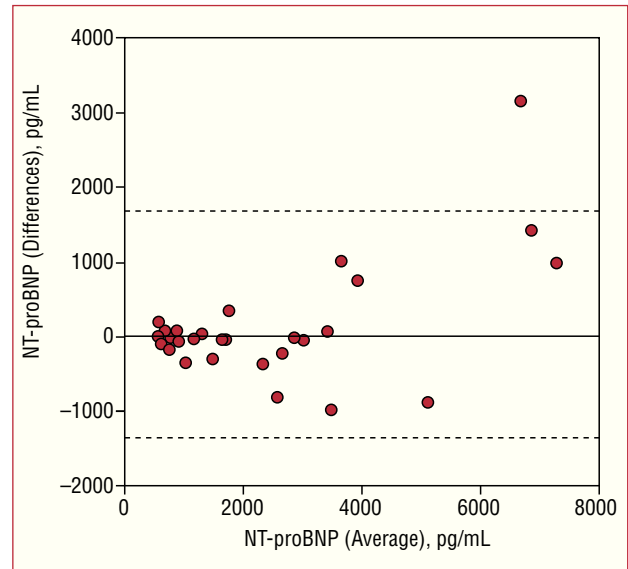


Figure. Bland-Altman plot for NT-proBNP.

NT-proBNP indicates the N-terminal peptide of pro-B-type natriuretic peptide.

used to demonstrate clinical stability. It may be necessary to determine whether other peptides show a similar correlation with NT-proBNP in patients under the same conditions.

In conclusion, the concentrations of NT-proBNP remain stable in patients with stable heart failure as a result of systolic dysfunction, especially in patients with a lower functional class.

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