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Does NT-proBNP Remain a Sensitive Biomarker for Chronic Heart Failure after Administration of a Beta-blocker?

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Summary

Background: Beta-blockers exert complex effects on plasma N-terminal-pro-B-type natriuretic peptide (NT-proBNP) level.

Hypothesis: We aimed to investigate whether NT-proBNP was still able to mirror the severity of chronic heart failure and predict the prognosis of the disease after administration of a beta-blocker.

Methods: Forty-four patients with chronic congestive heart failure were enrolled in the study to randomly receive carvedilol or bisoprolol in addition to background therapy. These patients underwent clinical measurement and blood sampling for NT-proBNP measurement at baseline and 3 or 7 months after the addition of the beta-blocker. The patients were followed-up for 3 years in order to register the occurrence of all-cause death.

Results: NT-proBNP level showed a positive correlation with the severity of heart failure as evaluated by New York Heart Association (NYHA) classification both before and after administration of either beta-blocker. The relationship between NT-proBNP and NYHA class was not weakened with the duration of therapy. Furthermore, NT-proBNP was the only independent predictor of all-cause mortality both before and after administration of either beta-blocker. Left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVEDD), age, NYHA class and treatment group were not independently predictive of mortality in this study.

Conclusions: The ability of NT-proBNP to reflect the severity and to predict the endpoint in chronic heart failure is not undermined after administration of a beta-blocker, suggesting that NT-proBNP remains a sensitive biomarker for chronic heart failure both before and after administration of a beta-blocker.

Key words: natriuretic peptide, brain, heart failure, congestive, adrenergic beta-antagonists

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Introduction

Neurohormonal activation is a hallmark of heart failure and influences its clinical evolution.[1] Various neurohormones have acted as biomarkers in chronic heart failure, but B-type natriuretic peptide (BNP) or N-terminal-pro-B-type natriuretic peptide (NT-proBNP) is the most widely embraced marker, particularly, given the availability of a rapid point-of-care assay.[2,3] Pro-BNP is synthesized in ventricular tissue in response to volume expansion and pressure overload, and then the two fragments of Pro-BNP, i.e. BNP and NT-proBNP, are cosecreted to plasma.[3,4] Compared with BNP, NT-proBNP has a higher molecular weight and shows a lower *in vivo* and *in vitro* degradation, resulting in a better reproducibility and functional sensitivity.[5] Prior studies have indicated that plasma NT-proBNP concentration is a sensitive marker for the severity and prognosis of patients with chronic heart failure.[6–8] Treatment guided by the plasma NT-proBNP concentration has been shown in a prior study to be superior to conventional treatment guided by physical findings, chest roentgenography, and electrocardiography.[9] However, A potential weakness of the above studies was the low rate of beta-blocker use.

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The effect of beta-blockers on plasma natriuretic peptide has been reported in different clinical diseases. The reported responses are widely divergent.[10–16] It implies that beta-blockers might exert complex effects on plasma natriuretic peptide, the underlying mechanism of which remains to be clear. This finding raises the question whether NT-proBNP remains a sensitive biomarker for the severity and prognosis of patients with chronic heart failure under beta-blocker treatment. The purpose of the study was to elucidate the correlates of NT-proBNP with the severity and prognosis of patients with chronic heart failure both before and after administration of a beta-blocker.

Methods

Patients

Patients were considered eligible for the study if they had stable chronic congestive heart failure for more than 3 months, and they had left ventricular ejection fraction (LVEF) less than 40%. In addition, study patients had to be clinically stable under the therapy of digoxin, diuretics, and angiotensin-converting enzyme inhibitors (ACEI) for more than 2 weeks before the study. Subjects were excluded if: (i) their resting heart rate was <65 beats per minute; (ii) their systolic blood pressure was <95 mmHg, or their diastolic blood pressure was <58 mmHg; (iii) they had contraindications for beta-blocker use such as obstructive pulmonary disease and renal dysfunction. (iv) They had unstable angina or myocardial infarction within 2 months; (v) they were currently treated with a beta-blocker. All subjects gave written informed consent, and the study was approved by the local ethics committee.

Study Protocol

After baseline clinical measurements, which included assessment of symptoms, LVEF by echocardiography using Simpson's modified method, and blood sampling, patients were randomized to receive treatment either with bisoprolol or carvedilol in addition to background therapy. There was a titration period, increasing the dose of carvedilol from 6.25 to 50 mg per day and bisoprolol from 2.5 to 10 mg per day. The dose was uptitrated each 10 ± 3 days if the prior dose was clinically tolerated. Mean maintenance doses were 43.75 mg for carvedilol and 8.47 mg for bisoprolol. The whole randomized trial period was 7 months. At the end of 3 and 7 months, clinical measurements and blood sampling were repeated. The patients were followed-up for 3 years for all-cause mortality.

Measurement of NT-proBNP

Venous samples for NT-proBNP assay were drawn into cooled tubes, promptly centrifuged and the separated plasma frozen to -20°C until assay. Plasma NT-proBNP concentrations were measured by a fully automated electrochemiluminescence "sandwich" immunoassay on Elecsys 2010 analyser (Roche Diagnostics). The clinicians involved with the patients' care were blinded to the NT-proBNP values obtained.

Statistic

All data were described as mean $\pm$ standard deviation, unless otherwise specified. Baseline characteristics were analyzed by the unpaired t-test or chi-squared test (for nonparametically distributed values). Because NT-proBNP values are not normally distributed, natural logarithmic transformation of data was used for statistical analysis when needed. The significance of changes in NT-proBNP levels, LVEF, left ventricular end diastolic diameter (LVEDD) and heart rate was evaluated using the paired Student's t-test. The Wilcoxon signed rank test was used to test for changes between 2 periods in New York Heart Association (NYHA) class. Bivariate correlations were assessed using nonparametric Spearman correlation coefficient. Univariate and stepwise multivariate Cox proportional hazard analyses were performed to investigate the relationship between NT-proBNP and 3-year mortality from any cause. 6 Variables were used: age, LVEF, LVEDD, NT-proBNP plasma level, NYHA class, treatment group: (i) at baseline, and (ii) at 7 months after initiation of beta-blocker. A p-value <0.05 was considered statistically significant.

Statistical analysis was performed by SPSS for windows, version 13.0 software (SPSS Inc, Chicago, Illinois).

Results

Patient Characteristics

Forty-four patients were enrolled in the study, randomized to bisoprolol and carvedilol. They were mainly men with NYHA class II–IV heart failure treated with diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and digoxin. There were no differences in baseline characteristics between the two treatment groups. The clinical characteristics were summarized in Table 1.

During the randomized trial period, 2 patients on bisoprolol underwent exacerbation of heart failure requiring hospitalization, and 1 patient on carvedilol died from exacerbation of heart failure.

TABLE 1 Clinical characteristics of the study population

	Bisoprolol (n = 22)	Carvedilol (n = 22)	All
Age (years)	60.1 ± 10.0	59.6 ± 11.4	60.0 ± 10.6
Sex (m/f)	17/5	16/6	33/11
NYHA functional class (n)			
II	8 (36.4%)	6 (27.3%)	14 (32%)
III	12 (54.5%)	16 (72.7%)	28 (64%)
IV	2 (9.1%)	0	2 (5%)
Concomitant medications			
Digoxin (%)	63.6%	86.4%	75.0%
Diuretics (%)	90.9%	86.4%	88.6%
ACEI (%)	86.4%	86.4%	86.4%
ARB (%)	4.5%	9.1%	6.8%
LVEF (%)	27.7 ± 6.2	29.0 ± 7.0	28.3 ± 6.6
LVEDD (mm)	69.9 ± 5.7	73.8 ± 9.5	71.8 ± 8.0

The values are expressed as the mean ± standard deviation or number (%) of patients. There were no differences in baseline characteristics between the two treatment groups. NYHA = New York Heart Association, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end diastolic diameter.

Effects of Carvedilol or Bisoprolol on Clinical Measurements and Left Ventricular Systolic Function

The results of the heart rate, NYHA class, LVEF and LVEDD at baseline, 3 months, and 7 months are shown in Table 2. Both beta-blockers produced a sustained and significant improvement in symptoms and left ventricular systolic function. There was no difference between the carvedilol group and the bisoprolol group in the above parameters throughout the study period.

NT-proBNP Measurements

Figure 1 shows the NT-proBNP measurements at baseline and after 3 and 7 months of beta-blocker therapy. There were significant reductions in NT-proBNP levels after 3 months by either beta-blocker compared with baseline ($p = 0.009$). The reductions remained significant after 7 months of therapy with either beta-blocker ($p = 0.007$). There was no difference between the carvedilol group and the bisoprolol group in NT-proBNP levels throughout the study period.

Correlation Between NYHA Classes and NT-proBNP Before and After Beta-blocker Therapy

NYHA classes decreased during the 7 months of beta-blocker. At baseline and at 3 and 7 months after initiation of beta-blocker, mean NT-proBNP levels were significantly higher in patients with higher NYHA class (Fig. 2A, B, C), and the relationship became progressively stronger with the duration of therapy (Table 3).

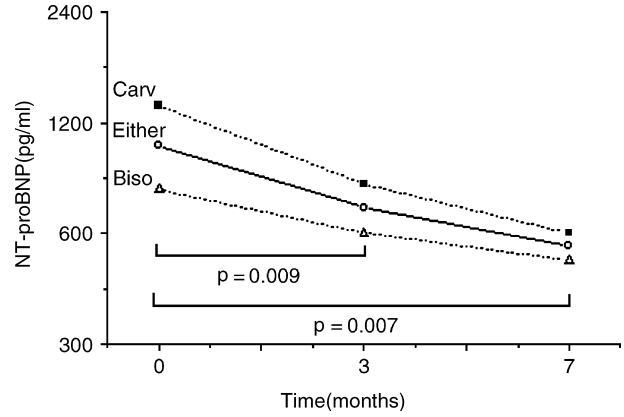

FIG. 1 Changes in plasma levels of NT-proBNP (expressed on a log scale) from baseline to 3 and 7 months after beta-blocker therapy. Carv = carvedilol; Biso = bisoprolol. *T*-test comparison of natural log-transformed NT-proBNP.

Prognostic Significance of NT-proBNP Preceding 3-year Mortality Before and After Beta-blocker Therapy

During 3 years of follow-up, 8 of the 44 patients died. The usefulness of various variables measured at baseline and at 7 months in predicting 3-year prognosis for all-cause mortality was investigated. At baseline, only NT-proBNP was significantly associated with the endpoint to death in univariate Cox analysis. At 7 months, the significant univariate predictors of outcome were NT-proBNP and NYHA class. Treatment modality had no significant effect either at baseline or at 7 months (Table 4).

In the next step, stepwise(forward) multiple Cox analysis was performed using the above univariate factors. NT-proBNP remained the only independent predictor of outcome both at baseline and at 7 months after initiation of either beta-blocker.

Discussion

Beta-blocker therapy has been established as standard therapy of chronic heart failure after trials showing a reduction in mortality in all NYHA classes of systolic heart failure.[17–19] The effect of a beta-blocker on plasma natriuretic peptide has been previously demonstrated in population-based studies, in healthy control studies, during exercise, in hypertension, in coronary disease, and in heart failure.[10–13,20] NT-proBNP increased in parallel with decreased heart rate in atenolol-treated hypertensive patients whereas it decreased in parallel with blood pressure in losartan-treated patients in the study by Olsen *et al.*[13] As for the patients with chronic

TABLE 2 Effects of carvedilol or bisoprolol on clinical measurements and left ventricular systolic function

	Bisoprolol			Carvedilol		
	Baseline	Month 3	Month 7	Baseline	Month 3	Month 7
Heart rate (beats/min)	76.9 ± 11.2	64.7 ± 8.0^b	68.8 ± 8.2^b	76.3 ± 11.0	67.6 ± 9.1^b	72.7 ± 8.6
NYHA class	2.7 ± 0.6	2.1 ± 0.5^b	1.9 ± 0.9^a	2.7 ± 0.5	2.1 ± 0.5^b	1.7 ± 0.7^b
LVEF(%)	27.7 ± 6.2		41.8 ± 8.0^b	29.0 ± 7.0		38.2 ± 9.3^b
LVEDD (mm)	69.9 ± 5.7		66.2 ± 6.6^a	73.8 ± 9.5		70.2 ± 9.0^b

[a] Represent $p<0.05$ vs. baseline.
[b] Represent $p<0.01$ vs. baseline.

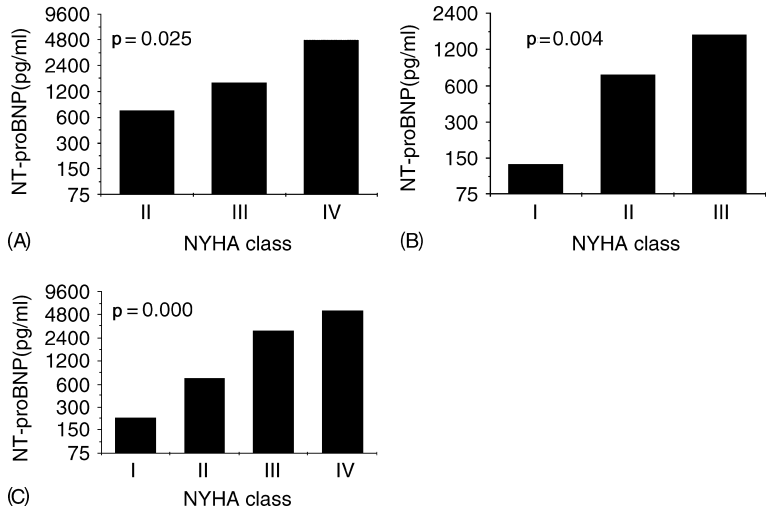

FIG. 2 A,B,C, Relationship between NT-proBNP (expressed on a log scale) and NYHA class at baseline and at 3 and 7 months after initiation of either beta-blocker.

TABLE 3 Correlation between NT-proBNP and NYHA class at baseline and at 3 and 7 months after initiation of either beta-blocker

NT-proBNP	NYHA class
Baseline	$r = 0.426$
p-value	0.004
3 Months	$r = 0.483$
p-value	0.002
7 Months	$r = 0.639$
p-value	0.000

heart failure, the results of studies that have measured plasma natriuretic peptide during beta-blockers therapy are widely divergent, especially when treatment period is short. Davis *et al*. reported that NT-proBNP and BNP increased at 6 weeks after the introduction of metoprolol in heart failure.[14] They explained that the early effects of a beta-blocker, including longer cardiac filling times and negative inotropism, might increase wall stress, and thus stimulate secretion of natriuretic peptide from the left ventricular. However, several other studies have presented opposite findings.[15,16]

On the other hand, it appears that a longer duration of beta-blocker therapy is more likely to be associated with declining natriuretic peptide levels, perhaps reflecting further decline in cardiac filling pressures and incremental effects on remodeling. In our study, the plasma level of NT-proBNP was decreased after a 3-month therapy with a beta-blocker, and the decrease tended to be greater at 7 months. Thus, our results support previous data suggesting that prolonged treatment with beta-blockers decreases plasma NT-proBNP levels.

It is obvious that beta-blockers exert complex effects on plasma NT-proBNP concentration. The observed decrease in NT-proBNP level in our study might be a direct result of an interaction between complex effects exerted by beta-blocker. The underlying mechanism remains to be clear. However, from a clinical point of view, it is more important to know whether plasma NT-proBNP concentration in this setting can still reflect severity of heart failure and predict prognosis of the disease, for NT-proBNP has been proposed as a diagnostic tool and prognostic marker in chronic heart failure.

TABLE 4 Cox univariate analysis of various variables measured at baseline and at 7 months—predicting outcome

	At baseline			At 7 months		
	χ^2	p	HR	χ^2	p	HR
Age (per 1 year)	2.438	0.118	1.060	0.721	0.396	1.039
LVEF (per 1%)	2.959	0.085	0.894	3.510	0.061	0.909
LVEDD (per increase in 1 mm)	0.357	0.550	0.971	0.004	0.949	1.003
NT-proBNP (per increase in 1000 pg/mL)	9.150	0.002	1.306	8.691	0.003	1.353
NYHA class (per increase in one class)	0.920	0.337	2.007	6.750	0.009	4.006
Treatment group (carvedilol vs. bisoprolol)	0.513	0.474	0.593	0.351	0.554	0.582

HR = hazard ratio.

In our study, we investigated the ability of NT-proBNP to mirror the severity of chronic heart failure as evaluated by NYHA classification before and after administration of a beta-blocker. Our results indicated that NT-proBNP levels showed a positive correlation with NYHA classification, and the relationship became progressively stronger with the duration of beta-blocker therapy. It suggests the plasma NT-proBNP concentration under long-term influence of beta-blocker can still mirror the severity of heart failure.

Furthermore, we investigated the relation of NT-proBNP to the 3-year mortality. NT-proBNP emerged as the superior modality, indeed it was the only independent predictor of all-cause mortality both before and after administration of a beta-blocker. These results indicated beta-blockers might exert a neutral effect on the prognostic value of NT-proBNP. We did not find either the LVEF, LVEDD, age or NYHA class to be independent predictors of death. This may, of course, be due to the relatively small numbers of deaths in our study.

Limitation

There is no placebo control group, and so it is possible that factors other than beta-blockers could have contributed to the observed findings. However, all patients were on background anti-heart failure therapy before the addition of either beta-blocker, and so we believe that the findings can be attributed to effects of beta-blockers. A placebo-controlled design would be unethical, because beta-blockade represents current standard of care for chronic heart failure. Another limitation was the small number of study patients. We are aware that a larger number of subjects would have improved the reliability of our results.

Conclusions

NT-proBNP levels showed a positive correlation with the severity of heart failure as evaluated by NYHA classification both before and after addition of a beta-blocker to background anti-heart failure therapy. Furthermore, the ability of NT-proBNP to predict all-cause death was not undermined after administration of a beta-blocker. These results suggest that NT-proBNP remains a sensitive biomarker for chronic heart failure both before and after administration of a beta-blocker.

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