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Relation of Body Fluid Status to B-Type Natriuretic Peptide Levels in Patients with Chronic Heart Failure during Long-Term Follow-Up

HAJIME KATAOKA, M.D.

Department of Internal Medicine, Nishida Hospital, Oita, Japan

Summary

Background: Little is known about the relationship of body fluid status with the levels and fluctuations of B-type natriuretic peptide (BNP) over the long term.

Hypothesis: If BNP is to become useful for monitoring of patients with chronic heart failure (HF), the levels should reliably reflect both decompensation and improvement in the patient's condition.

Methods: Forty-six patients with chronic HF who were stable at study entry but had previous decompensation were recruited and followed up between June 2003 and September 2005. At each visit, they were examined for BNP level and HF-related signs of body fluid retention based on physical evaluation and pleural ultrasonography.

Results: During the study period, 26 patients developed decompensation and 20 maintained a stable clinical course. In the 26 decompensated patients, BNP levels fluctuated widely (110 ± 73.7 pg/ml; range 25–290 pg/ml) even during stable periods. In all but three patients in this group, the maximum BNP level during decompensation was higher than that reached during stable periods. The BNP levels also fluctuated widely (180 ± 123 pg/ml; range 16–489 pg/ml) in the 20 stable patients with HF. In all but one patient in this group, the BNP level was lower than the maximum BNP level obtained during the previous decompensation.

Conclusions: In patients with chronic HF with previous decompensation, there was a strong link between the appearance of clinical HF sign(s) of fluid retention and an increased BNP level despite wide intraindividual fluctuations in BNP over time. Thus, BNP levels reliably reflect both decompensation and improvement.

Key words: B-type natriuretic peptide, ultrasonography, heart failure, physical sign, pleural effusion

Introduction

B-type natriuretic peptide (BNP) is released by the failing heart in proportion to the increase in cardiac filling pressure.[1] Levels of BNP reflect the severity of the hemodynamic parameters[2, 3] and correlate with the New York Heart Association (NYHA) classification[4] of patients with heart failure (HF). Plasma BNP and N-terminal (NT)-proBNP levels, however, are highly dynamic, likely nonlinear, and highly complex.[5] The variability of plasma BNP and NT-proBNP levels have been explored,[6, 7] but the determinants that govern these peptide levels in patients with HF are still under investigation.[7]

If BNP is to become useful for monitoring of patients with chronic HF, the levels should reliably reflect both decompensation and improvement in the patient's condition. Because of the episodic nature of HF decompensation, periodic changes in body fluid status in patients with HF should affect the BNP level. In patients with chronic HF, however, little is known about the relationship of body fluid status with the levels and fluctuations of BNP over the long term.[6–8] The main purpose of this study was to examine the longitudinal relationship between clinically determined body fluid status and BNP level in patients with chronic HF (1) to explore the intra individual fluctuations in plasma BNP levels over time and (2) to determine whether the levels reliably reflect both decompensation and improvement in the individual patient's condition.

Address for reprints:

Hajime Kataoka, M.D.
Internal Medicine
Nishida Hospital
3-3-24 Ohte-machi, Saiki-city
Oita 876-0831, Japan
e-mail: hkata@cream.plala.or.jp

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Methods

Study Population

This prospective study was performed in the outpatient clinic of Nishida Hospital (Oita, Japan) between June 2003 and September 2005. Patients were eligible for the trial if, upon study entry, they had stable chronic HF, presented with NYHA functional class II or III symptoms, and had no or minimal clinical evidence of HF-related signs. The study patients were required to have a previous history of decompensated HF with definite signs of fluid retention. In patients who presented with multiple episodes of HF during the study period, only data from the first episode were included. The protocol was approved by the ethics committee of Nishida Hospital, and all patients provided informed consent. Exclusion criteria included NYHA functional class IV symptoms at entry, recent acute coronary syndrome, moderate to severe pulmonary disease, or hepatic (serum bilirubin >2 mg/dl) or renal (plasma creatinine >2 mg/dl) insufficiency.

Study Protocol

Upon study entry, patient demographics, history, NYHA functional class, primary etiology, physical and laboratory examination results, and drug prescriptions were recorded. At every clinic visit, each patient was thoroughly examined by the same cardiologist (H.K.) for BNP level, symptoms, and HF-related signs of body fluid retention based on physical evaluation and pleural ultrasonography.[9, 10] B-type natriuretic peptide was measured by the Shionoria assay method (inter- and intra-assay coefficients of variation 0.7%–1.4% and 2.8%–3.7%, respectively).[2] When new or worsening symptom(s) and/or sign(s) were identified, patients were further evaluated by optimal use of chest x-ray and/or echocardiography. Efforts were made to investigate the precipitating factors that led to HF decompensation.[11] Because a device for rapid measurement BNP levels[3] has not yet been approved at my hospital, the decision to change a therapeutic regimen was guided by clinical assessment described above other than BNP measurement. The primary endpoints of the trial included the appearance or worsening of HF-related symptoms, signs, and/or pleural effusion on an ultrasonogram.

Definition of Heart Failure Decompensation

There is no standard of reference for diagnosing HF decompensation, and the diagnostic criteria vary across studies.[5] In the present study, each patient served as his/her own control. Decompensation of chronic HF was clinically defined as the new appearance or worsening of HF-related symptom(s) and/or sign(s) compared with baseline stable clinical status evaluated at study entry. Main HF-related signs evaluated included pulmonary rales, peripheral edema, third heart sound on physical examination, and pleural effusion on an ultrasonogram.[9] Patients with decompensated HF were treated on an outpatient basis with the option to be hospitalized if clinically necessary. Physician review was used to determine whether treatment resulted in the return of clinical stability and a decrease in BNP level.

Statistics

Data are presented as the mean ± standard deviation unless otherwise indicated. Clinical characteristics of patients with and without decompensated HF were compared by Fisher's exact test. Continuous variables were analyzed using Student's *t*-test.

Results

Study Patients

In this prospective study, 57 patients with stable chronic HF in NYHA functional class II–III were recruited from the outpatient clinic between June 1, 2003, and June 30, 2005. Of these, 11 dropped out prior to the end of the trial, which ended on September 30, 2005. The results in the remaining 46 patients were analyzed for this study, and baseline characteristics are shown in Table I.

Development of Heart Failure Decompensation

The median duration of the present study was 248 days (range 24–1,124 days). The median interval between clinic

TABLE I Clinical characteristics

Characteristics	Number of patients (%)
Age (years)	78.1 ± 8.0
<65	4 (9)
65–75	9 (20)
>75	33 (71)
Male/female	14 (30) / 32 (70)
Etiology of heart failure	
Coronary artery disease	6 (13)
Arterial hypertension	10 (22)
Valvular heart disease	16 (35)
Dilated cardiomyopathy	8 (17)
Arrhythmia	4 (9)
Congenital heart disease	2 (4)
Atrial fibrillation	18 (39)
NYHA functional class II/III	34 (74) / 12 (26)
Medication	
Diuretics	45 (98)
ACE inhibitor/angiotensin II antagonist	20 (43)
Calcium antagonist	12 (26)
Beta blockers	27 (59)
Digitalis	8 (17)
Nitrates	8 (17)
Antiarrhythmics	5 (11)

Abbreviations: ACE = angiotensin-converting enzyme, NYHA = New York Heart Association.

visits for each patient was 35 days (range 15–79 days). During the study period, 26 patients developed decompensated HF and 20 maintained a stable clinical course.

Symptoms and Signs in Decompensated Patients

Of the 26 decompensated patients, 12 (46%) required an unplanned clinic visit because they noticed a worsening of HF-related symptom(s). At the point of HF decompensation, 42% of patients were not aware of symptomatic changes. At the point of clinically diagnosed decompensation, 14 patients (54%) had gained more than 2 kg compared with their most recent clinical visit.

Twenty-five decompensated patients (96%) demonstrated objective HF-related sign(s) under physical and ultrasonographic examinations. The remaining patient presented with HF-related symptoms and a body weight gain of more than 2 kg compared with the most recent clinical visit. Among the HF-related signs examined in the present study, pleural effusion on an ultrasonogram was the leading HF-related sign (77%), followed by rales (46%), edema (46%), and the appearance of a third heart sound (12%).

B-Type Natriuretic Peptides Levels in Decompensated Patients

The relationship of clinical HF status with plasma BNP levels during the follow-up in 26 decompensated patients is summarized in Figure 1. Circulating BNP levels fluctuated widely (110 ± 73.7 pg/ml; range 25–290 pg/ml, n = 24) during the stable periods. In all but three patients (Nos. 6, 18, and 20 in Fig. 1), circulating BNP levels obtained during stable periods were always lower than the maximum BNP value obtained during decompensation. Of the 26 decompensated patients, 13 (50%) demonstrated BNP levels of < 100 pg/ml during stable clinical periods.

Precipitating factors were identified in 18 (69%) of 26 patients with decompensated HF. The most common factors were poor compliance with the prescribed regimen or diet (23%) and excessive physical activity (19%). Other precipitating factors included the use of nonsteroidal anti-inflammatory drugs (12%), cardiac arrhythmias (12%), infection (8%), and alcohol consumption (4%).

Outcome of Decompensated Patients

Sixteen decompensated patients were managed on an outpatient basis and recovered from their deteriorated status by the next clinic visit. Of the other 10 hospitalized patients, 7 recovered from their decompensated status after therapy and 3 died of cardiac causes.

B-Type Natriuretic Peptide Levels in Stable Patients

During follow-up, none of the patients with stable chronic HF presented with new or worsening symptoms or HF-related signs. Circulating BNP levels during follow-up and maximum BNP values obtained at the time of previous decompensation are shown in Figure 2. Circulating BNP values fluctuated widely (180 ± 123 pg/ml; range 16–489 pg/ml) during the study period. In all patients except one in this group, circulating BNP levels were lower than the maximum BNP value obtained at the time of the previous HF decompensation. Of the 20 stable patients, 10 (50%) demonstrated BNP levels of < 100 pg/ml during the observation period.

Patients with Decompensated versus Stable Heart Failure

Compared with patients with HF and a stable clinical course, patients with decompensated HF more frequently presented with NYHA functional class III dyspnea at study entry, were less compliant regarding drugs, and visited the clinic at intervals that exceeded 60 days during follow-up (Table II).

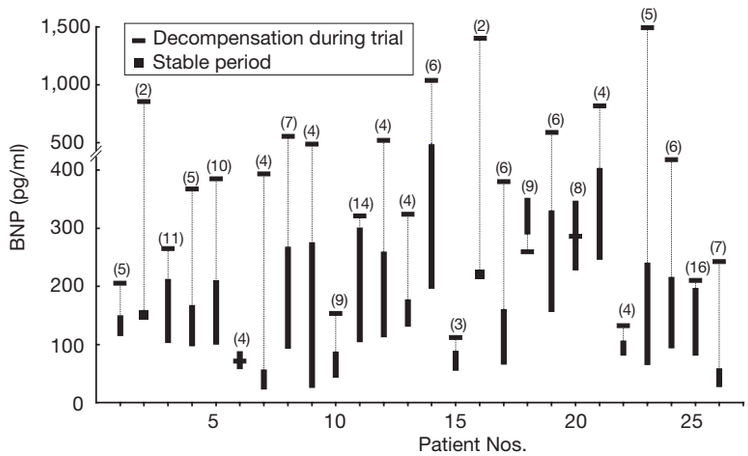

FIG. 1 B-type natriuretic (BNP) peptide levels during stable periods and the maximum value during decompensation in 26 patients with decompensated heart failure. The numbers in parentheses indicate the number of BNP determinations.

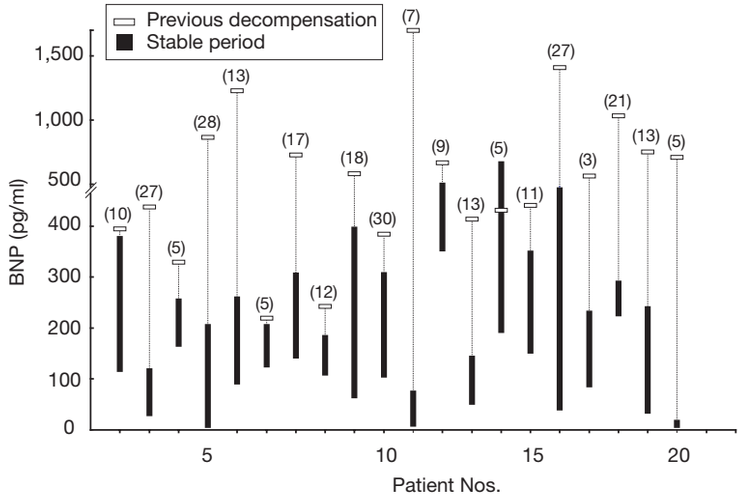

FIG. 2 B-type natriuretic peptide levels during stable periods and the maximum value during previous decompensation in 20 patients with stable heart failure.

TABLE II Patients with decompensated versus stable heart failure

Characteristics	Decompensated (n = 26)	Stable (n = 20)	p Value
Age (years)	78.2 ± 7.7	78.0 ± 8.5	NS
Male gender	10 (38)	4 (20)	NS
NYHA functional class III	11 (42)	1 (5)	<0.01
Follow-up (days)			
Duration	236 ± 144	468 ± 279	<0.001
Interval	41 ± 19	35 ± 10	NS
Interval >60 days	6 (23)	0	<0.05
Atrial fibrillation	11 (42)	7 (35)	NS
Maximum BNP level during stable periods	219 ± 113	284 ± 155	NS
Noncompliance with drugs or diet	6 (23)	0	<0.05

Values are mean ± standard deviation or number of patients (%).
Abbreviations: BNP = B-type natriuretic peptide, NYHA = New York Heart Association.

Discussion

Relationship of Body Fluid Status with Levels and Fluctuation of B-Type Natriuretic Peptide

There are few data on the fluctuation or variability of BNP levels over time in patients with chronic HF. Bruins *et al.*[7] investigated the intraindividual fluctuation of BNP and NT-proBNP in patients with stable chronic HF and reported that both peptides have high intraindividual variations over time. The relationship of clinically determined body fluid status with BNP levels, including both deterioration and stability, has not yet been fully evaluated in those patients. The present study examined the longitudinal relationship between clinically determined body fluid status and BNP levels in patients with chronic HF who were in an ambulatory care setting at the outpatient clinic. Accordingly, this study confirmed the previous observation by Bruins *et al.*[7] of wide BNP fluctuations during stable clinical conditions. Most important, this study demonstrated a strong link between body fluid retention during clinical deterioration and a rise in BNP levels. The latter observation, however, was not consistent with findings from the recent study by Lewin *et al.*,[8] in which changes in BNP during follow-up of patients with chronic HF were a poor predictor of HF deterioration. The explanation for this difference between the two studies remains unclear, but the different approach used for diagnosing clinical deterioration or stability may have contributed. In the present study, the addition of thoracic ultrasonography[9] to standard physical examination may have yielded more accurate identification of patients with decompensated HF based on the objective sign of fluid retention, thus demonstrating the intimate relationship between changes in BNP levels and clinical HF deterioration. In contrast, many patients in the study by Lewin *et al.*[8] were in a state of deterioration based on symptomatic criteria. There are conflicts concerning the correlation of BNP with HF-related symptoms.[12]

It is hypothesized that the BNP level of a patient who is admitted with decompensated HF is composed of two components: a baseline, euvolemic "dry" BNP level and a level induced by acute pressure or volume overload ("wet" BNP level).[1] The present study supports this hypothesis and confirmed that changes in BNP levels reliably reflect the condition of the patient with HF, "wet" or "dry," of body fluid status. Plasma BNP levels corresponding to each condition may, however, vary in individual patients with HF according to the underlying clinical condition as shown in this study, and any BNP levels in patients with chronic HF must be interpreted in light of whether this patient is at optimum volume status.[13] During stable clinical periods, half of the patients with HF in

the present study demonstrated BNP levels of < 100 pg/ml (levels that are often considered "normal" in contemporary diagnosis) despite having a history of decompensation, as reported in previous studies.[14, 15]

Determinants of B-Type Natriuretic Peptide Levels

The determinants that govern plasma BNP and NT-proBNP levels in patients with HF are presently under investigation.[7] The course of HF is episodic, and at the time of referral some patients were in transient "decompensated" HF, which then became "compensated." Considering the episodic nature of chronic HF, the present study suggests that wide fluctuations in BNP levels during the follow-up of patients with HF are associated with periodic precipitating factors,[11] as typically observed in decompensated patients in this study, that would lead to episodic body fluid retention, thus affecting the BNP fluctuation in an individual patient with HF. The effect of blood volume status on plasma BNP levels has been examined previously in a small number of patients with HF.[16, 17] Left ventricular dilatation induced by body fluid retention, via its effect on wall stress, may be an important mechanical factor stimulating BNP release in these patients.[18] Other factors that should be taken into consideration include the multiple variables involved in the homeostasis of BNP in an individual patient with HF, from gene transcription to cellular secretion, metabolism, clearance, age, and obesity, all of which can affect the final value and fluctuation of BNP.[19–21]

Limitations

The major limitation of the present study is the lack of a standard of reference for diagnosing chronic HF decompensation;[5] each patient served as his/her own control, that is, baseline stable clinical status of each individual patient at study entry was defined as the clinical "reference standard" of acute HF decompensation. Second, this study was performed in a small sample of patients with HF of various etiologies, most of whom were over 65 years of age. Third, without objective hemodynamic measurements, such as obtained using an implantable hemodynamic monitor,[16] one cannot assess the significance of the fluctuation in BNP during periods of apparent clinical stability. It is entirely possible that left ventricular filling pressure varied substantially in the "stable" periods. Fourth, all patients were in NYHA functional class II and III subsets. The impact of including patients with more advanced HF on the present findings remains to be determined.

Conclusion

In patients with chronic HF with previous decompensation, there was a strong link between the appearance of clinical HF sign(s) of fluid retention and an increased BNP level despite wide intraindividual fluctuations in BNP over time. Thus, BNP levels reliably reflect both decompensation and improvement.

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