Correlates of NT-proBNP Concentration in Patients With Essential Hypertension in Absence of Congestive Heart Failure

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Background: N-terminal proBNP (NT-proBNP) is widely used as a diagnostic biomarker and for the risk stratification of patients with heart failure (HF). Its role in the evaluation of patients with essential hypertension (EHT) is less clear. We examined the relationship between NT-proBNP concentrations and various clinical characteristics in hypertensive patients without HF. **Methods:** This study included 186 consecutive patients with EHT and no history of HF, ischemic heart disease, or atrial fibrillation. Single and multiple variable regression analyses were performed in search of clinical correlates of NT-proBNP concentrations. **Results:** In patients with EHT, median serum concentration of NT-proBNP was 73 pg/ml, and interquartile range (IQR) was 40–128 pg/ml. NT-proBNP was significantly higher ($P < 0.001$) in women (87 pg/ml; IQR

55–137 pg/ml) than in men (52 pg/ml; IQR 24–115 pg/ml). Age ($r = 0.371$, $P < 0.001$), precordial QRS voltage ($r = 0.223$, $P < 0.001$), hemoglobin (Hgb) concentration, ($r = -0.208$, $P = 0.023$) and estimated glomerular filtration rate ($r = -0.139$, $P = 0.044$) were correlated with log-transformed NT-proBNP by multiple variable analysis. In men, age ($r = 0.453$, $P < 0.001$) and QRS voltage ($r = 0.283$, $P = 0.004$), and in women age ($r = 0.299$, $P = 0.006$), QRS voltage ($r = 0.212$, $P = 0.019$), Hgb ($r = -0.182$, $P = 0.049$), and estimated glomerular filtration rate ($r = -0.272$, $P = 0.009$) were correlated with serum concentrations of NT-proBNP. **Conclusions:** Age, gender, Hgb, left ventricular hypertrophy and renal function were correlated with NT-proBNP in patients with EHT. *J. Clin. Lab. Anal.* 24:12–16, 2010. © 2010 Wiley-Liss, Inc.

Key words: natriuretic peptide; hypertension; aging; gender; anemia; renal failure; hypertrophy; electrocardiography; biomarker

INTRODUCTION

B-type natriuretic peptide (BNP), released predominantly from the ventricular myocardium in response to increased ventricular wall stress (1,2), is widely used as a diagnostic biomarker and in the risk stratification of patients suffering from heart failure (HF) (3). In hypertensive patients, the blood concentrations of BNP are higher than in normotensive subjects (4,5), and predict the risk of adverse cardiovascular events (6). In patients with HF, the blood concentration of BNP varies also with age, gender, hemoglobin (Hgb), body mass index, and renal function (7,8).

N-terminal proBNP (NT-proBNP) is the physiologically inactive 76 amino acid fragment, which is secreted with the 32 amino acid BNP, after cleavage from proBNP (9). Therefore, NT-proBNP is produced in

equivalent molar concentrations as BNP. However, in the presence of HF, the serum half-life of NT-proBNP is longer and more dependent on renal function than that of BNP (10). The recent study by van kimmenade et al. provides possible mechanism to explain increased NT-proBNP and BNP concentration (11). NT-proBNP and BNP are equally dependent on renal function for their clearance in hypertensive patients, but NT-proBNP rises disproportionately to BNP at lower renal function.

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There is still uncertainty about the effect of renal function on concentration of both NT-proBNP and BNP.

In patients presenting with essential hypertension (EHT), the serum concentrations of NT-proBNP are slightly or moderately higher than in normotensive subjects (12,13). However, the clinical role played by NT-proBNP, and the significance of an elevated NT-proBNP are both unclear. Furthermore, the factors that influence the serum concentrations of NT-proBNP in patients with EHT are mostly unknown. The objective of our study was to examine the relationship between NT-proBNP concentrations and various clinical characteristics in patients suffering from EHT in the absence of congestive HF.

STUDY POPULATION AND METHODS

This study included 186 consecutive patients suffering from EHT, defined as a systolic pressure 140 mmHg, diastolic pressure 90 mmHg, or both, before the onset of treatment with blood pressure pressure-lowering drugs. The patients had no history of HF, ischemic heart disease, or atrial fibrillation. Blood pressure measurements were made and electrocardiograms recorded in our ambulatory department. Venous blood was collected at the time of examination. The study procedures were in compliance with the guidelines of the Hyogo prefecture Amagasaki Hospital.

Study Measurements

Venous blood was collected for measurements of NT-proBNP, creatinine, serum sodium (Na), serum potassium (K), and Hgb concentrations. Serum

concentrations of NT-proBNP were measured, using a highly sensitive and specific immunoassay based on a double antibody sandwich technique (Roche Diagnostics, Tokyo Japan). The estimated glomerular filtration rate (eGFR) was calculated as:

$$\text{Men: } 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$$

$$\text{Women: } 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739.$$

The severity of left ventricular hypertrophy (LVH) was assessed by the sum of the S wave in lead V1 + R wave in lead V5 or V6 voltage (Sokolow–Lyon voltage), measured on the 12-lead surface electrocardiogram.

Statistical Analysis

The distributions of clinical characteristics are expressed as medians and 25th–75th interquartile range (IQR) and means $\pm$ standard deviation (SD). Because of a skewed distribution of NT-proBNP, a common log transformation was used in the regression analysis. Multiple variable regression analysis was used to identify variables independently correlated with the log-transformed NT-proBNP concentration. Differences between men and women were examined, using the Mann–Whitney *U*-test. A *P* value < 0.05 was considered statistically significant. All statistical analysis was performed using the Statview software, version 5.0 (SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics

Table 1 shows the characteristics of the 186 patients included in the study. Their mean age was 67.3 ± 10.9 years; the mean age of the 101 women was 68.8 ± 10.9 years and that of the 85 men was 65.5 ± 10.6 years.

TABLE 1. Characteristics of the Study Population

Characteristic	All patients (n = 186)			Men (n = 85)			Women (n = 101)		
	Median	25th–5th (IQR)	Mean $\pm$ SD	Median	25th–75th (IQR)	Mean $\pm$ SD	Median	25th–5th (IQR)	Mean $\pm$ SD
Age, y	69	60–75	67.3 ± 10.9	67	59–73	65.5 ± 10.6	72	59–77	68.8 ± 10.9
NT-proBNP, pg/ml*	73	40–128	108 ± 127	52	24–115	95 ± 137	87	55–137	119 ± 118
Estimated glomerular filtration rate, ml/min/1.73m ²	66	55–77	67 ± 16	67	57–74	67 ± 15	64	53–78	67 ± 18
Hemoglobin, g/dl**	13.3	12.6–14.4	13.4 ± 1.4	14.3	13.6–15.0	14.2 ± 1.4	13.0	12.1–13.3	12.7 ± 1.1
Serum sodium, mEq/l	141	140–143	141 ± 2	141	139–143	141 ± 2	141	140–142	141 ± 2
Serum potassium, mEq/l	4.0	3.8–4.2	4.0 ± 0.3	4.0	3.8–4.3	4.0 ± 0.4	4.0	3.8–4.2	4.0 ± 0.3
SV1+RV5 (6), mV	2.7	2.1–3.3	2.8 ± 1.0	2.8	2.2–3.5	3.0 ± 1.1	2.7	2.1–3.2	2.7 ± 0.9
Blood pressure, mmHg									
Systolic	136	124–148	138 ± 20	139	125–150	141 ± 21	135	121–148	136 ± 19
Diastolic***	80	71–86	80 ± 12	82	72–89	82 ± 14	78	70–87	77 ± 10

Values are expressed as median with interquartile (25th–75th) and mean $\pm$ SD. *NT-proBNP was significant higher in female than in male by Mann–Whitney test ($P < 0.001$). **Hemoglobin was significant higher in male than in female by Mann–Whitney test ($P < 0.001$). ***Diastolic blood pressure was significant higher in male than in female by Mann–Whitney test ($P = 0.035$).

In the overall population, the median NT-proBNP was 73 pg/mL (IQR: 40–128 pg/mL). The NT-proBNP concentration was significantly higher ($P < 0.001$) in women (median = 87 pg/mL; IQR: 55–137 pg/mL) than in men (median = 52 pg/mL; IQR: 24–15 pg/mL; Fig. 1), the mean Hgb concentration was significantly lower ($P < 0.001$) in women (12.7 ± 1.1 g/dL) than in men (14.2 ± 1.4 g/dL).

Correlation between NT-proBNP and Clinical Characteristics

The outcomes of the single variable regression analysis are shown in Table 2 and Figure 2. Within the entire study population, the log-transformed NT-proBNP concentration was positively correlated with age ($r = 0.485$, $P < 0.001$), negatively correlated with Hgb concentration ($r = -0.371$, $P < 0.001$) and eGFR ($r = -0.309$, $P < 0.001$), and weakly correlated with SV1 + RV5 (6) voltage ($r = 0.201$, $P = 0.008$) and serum sodium concentration ($r = 0.149$, $P = 0.042$). There was no correlation between NT-proBNP and blood pressure. In men, log-transformed NT-proBNP was correlated with age ($r = 0.480$, $P < 0.001$), Hgb ($r = -0.290$, $P = 0.007$), eGFR ($r = -0.257$, $P = 0.018$), and SV1 + RV5 (6) voltage ($r = 0.300$, $P = 0.007$). In women,

Fig. 1. Distribution of NT-proBNP concentrations in men vs. women. The population was divided among five ranges of serum concentrations. The median NT-proBNP concentration in men was 52 pg/mL (IQR: 24–15), vs. 87 pg/mL (IQR: 55–137) in women ($P < 0.001$; Mann-Whitney *U*-test).

log-transformed NT-proBNP was correlated with age ($r = 0.468$, $P < 0.001$), Hgb concentration ($r = -0.294$, $P = 0.003$), and eGFR ($r = -0.396$, $P < 0.001$).

When the factors found significant by single variable analysis were entered in the multiple variable regression model, age ($r = 0.371$, $P < 0.001$), SV1 + RV5 (6) voltage ($r = 0.223$, $P < 0.001$), Hgb concentration ($r = -0.208$, $P = 0.023$), and eGFR ($r = -0.139$, $P = 0.044$) were independently correlated with log-transformed NT-proBNP. Age ($r = 0.453$, $P < 0.001$) and SV1 + RV5 (6) voltage ($r = 0.283$, $P = 0.004$) were correlated with NT-proBNP concentration in men, and age ($r = 0.299$, $P = 0.006$), SV1 + RV5 (6) voltage ($r = 0.212$, $P = 0.019$), Hgb ($r = -0.182$, $P = 0.049$), and eGFR ($r = -0.272$, $P = 0.009$) were correlated with NT-proBNP concentration in women (Table 3).

DISCUSSION

NT-proBNP is widely used as a diagnostic marker and risk stratifier in patients suffering from HF, though several studies have reported variations in serum NT-proBNP concentrations according to age, gender, renal function, body mass index, and serum Hgb concentration (14,15). In patients with EHT, the concentrations of NT-proBNP are (a) slightly or moderately higher than in normotensive subjects (12,13), and (b) a predictor of adverse cardiac events (4). In a recent study by Van Kimmenade et al., (11) the NT-proBNP concentration independently associated with mean arterial pressure, hematocrit, GFR, renal plasma flow, left ventricular ejection fraction, and left ventricular mass index. In this study, we found correlation between NT-proBNP concentration and women, age, impaired renal function, low Hgb, and elevated voltage in SV1 + RV5 (6). (Figs. 1 and 2). Both study suggested, in patients with EHT, NT-proBNP were influenced various clinical characteristics as well as HF. However, there was a difference between prior study and our study. In our study, NT-proBNP concentration was not correlated with blood pressure, because blood pressure-lowering drug was not discontinued.

In a previous study of aging hypertrophied myocardium in rats, local ischemia caused a diffuse focal loss of

TABLE 2. Correlation Between NT-proBNP and Clinical Characteristics by Single Variable Regression Analysis

	All patients (<i>n</i> = 186)		Men (<i>n</i> = 85)		Women (<i>n</i> = 101)	
	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
Age	0.485	<0.001	0.480	<0.001	0.468	<0.001
Estimated glomerular filtration rate	-0.309	<0.001	-0.257	0.018	-0.396	<0.001
Hemoglobin	-0.371	<0.001	-0.290	0.007	-0.294	0.003
Serum sodium	0.149	0.042	0.180	0.100	0.119	0.234
SV1 + RV5 (6)	0.201	0.008	0.300	0.007	0.164	0.118

Fig. 2. Correlation between (a) NT-proBNP concentration and (b) age, Hgb, eGFR, or SV1+RV5 (6) voltage. (A) Age (x axis) was correlated ($r = 0.485$, $P < 0.001$) with NT-proBNP (y axis). (B and C) Hb concentration and eGFR (x axis) were both negatively correlated ($r = -0.371$ and $r = -0.309$, respectively: both $P < 0.001$) with log-transformed NT-proBNP (y axis). (D) SV1+RV5 (6) voltage (x axis) was weakly correlated ($r = 0.201$, $P = 0.008$) with log-transformed NT-proBNP (y axis).

TABLE 3. Correlation Between NT-proBNP and Clinical Characteristics by Multiple Variable Regression Analysis

	All patients (n = 186)		Men (n = 85)		Women (n = 101)	
	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
Age	0.371	<0.001	0.453	<0.001	0.299	0.006
Estimated glomerular filtration rate	-0.139	0.044	-0.065	0.507	-0.272	0.009
Hemoglobin	-0.208	0.023	-0.052	0.616	-0.182	0.049
SV1+RV5 (6)	0.223	<0.001	0.283	0.004	0.212	0.019

ventricular myocytes. As a result, the remaining myocytes suffered severe stress (16), which increased the production of NT-proBNP. In a study by Matsumoto et al., BNP concentrations were more strongly correlated with Hgb than with age, including in healthy subjects (17). Our study also suggested that the concentrations of Hgb are a strong correlate of NT-proBNP concentrations. This correlation is explained by the increase in plasma volume caused by anemia and the release of NT-proBNP in response to ventricular volume overload.

Furthermore, the concentration of Hgb was significantly lower in women than in men, whereas the reverse

was observed with respect to the NT-proBNP concentrations. This elevation of NT-proBNP in women is explained, at least partially, by the lower Hgb concentration. The elevated NT-proBNP concentration was also correlated with renal function. NT-proBNP is mainly cleared from the blood by the kidney, whereas BNP is mainly cleared by neutral endopeptidases and natriuretic peptide receptors (18). Therefore, renal dysfunction has a more prominent effect on the concentrations of NT-proBNP than of BNP.

In patients with EHT, LVH and NT-proBNP are independent predictors of adverse cardiovascular events

(6,13). A community-based study of 2,042 individuals without HF or renal failure found NT-proBNP concentrations below those observed in HF, which were prognostic markers after adjustment for traditional clinical risk factors. (4) In addition, in that study, which included 29% of hypertensive patients, NT-proBNP concentrations and LVH were correlated (4).

A previous study reported a weak correlation between BNP and the SV1+RV5 voltage (19). Our study also found a weak correlation between NT-proBNP concentration and SV1+RV5 (6) voltage, related to LVH. As since the diagnosis of LVH often requires echocardiography, which is expensive considering the size of the candidate population, it might be replaced by the simple and rapid measurements of NT-proBNP.

In summary, this study was to examine the relationship between NT-proBNP concentrations and various clinical characteristics in patients suffering from EHT in the absence of congestive HF. Our observations suggest that age, gender, Hgb concentrations, LVH, and renal function be considered when measuring NT-proBNP in EHT.

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