血液透析患者における血清ヒト脳性ナトリウム利尿ペプチド前駆体N端フラグメント

【Original Article】

Association between changes in serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and heart rate in hemodialysis patients

Shigeru OTSUBO[1)]　Nobuhiko JOKI[2)]　Yuri TANAKA[2)]　Takeshi NAKANISHI[3)]
Takahiro KURAGANO[3)]　Tomokatsu SAIJO[4)]　Hiroki HASE[2)]

Abstract

Background

An increase in the NT-pro-BNP level is reported to be a risk factor associated with mortality among hemodialysis patients. We investigated the change in NT-proBNP during a 12-month period and investigated factors capable of predicting changes in NT-proBNP among hemodialysis patients.

Methods

A total of 54 hemodialysis patients were enrolled. We set the baseline at 12 months after the start of the study and investigated the patient outcome during the subsequent 24 months. First, we investigated the risk factors (including the NT-proBNP ratio [baseline versus 12 months before the baseline]) associated with mortality. We also studied the relationship between the NT-proBNP ratio and several clinical factors at 12 months before the baseline.

Results

A univariate Cox proportional hazard analysis identified a high NT-proBNP ratio as a predictor of mortality (hazard ratio, 2.19; $P < 0.001$). Interestingly, the NT-proBNP ratio was positively correlated with the heart rate ($P < 0.001$).

Conclusion

We confirmed that an increase in NT-proBNP during a 12-month period, which was a relatively long observation period, was a risk factor associated with mortality in hemodialysis patients. We also found that the heart rate was a predictor of a change in the NT-proBNP level.

Key words：heart rate, hemodialysis, mortality, N-terminal pro-brain natriuretic peptide

Ⅰ. Introduction

Hemodialysis patients manifest significantly higher cardiovascular morbidity and mortality rates, compared with age-matched counterparts who are not receiving dialysis.[1)] As a novel biomarker for cardiovascular disease, brain natriuretic peptide (BNP) has received increasing attention.[2)] BNP belongs to a family of natriuretic peptides that plays a major role in the regulation of blood pressure and extracellular volume through the stimulation of natriuresis.[3)] BNP is produced by the ventricular myocardium in response to increased myocardial wall stress[4)] as a prehormone; upon release into

[1)] Department of Blood Purification, Sangenjaya Hospital, Tokyo, Japan
[2)] Department of Nephrology, Toho University Ohashi Medical Center, Tokyo, Japan
[3)] Division of Kidney and Dialysis, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan
[4)] Department of Nephrology, Saijo Clinic Takaban, Tokyo, Japan

the circulation, this prehormone is cleaved into a biologically active C-terminal fragment (BNP) and a biologically inactive N-terminal fragment (N-terminal pro-brain natriuretic peptide [NT-proBNP]).[5] The NT-proBNP concentration is a useful tool for screening for cardiac abnormalities in hemodialysis patients.[6) 7)] Furthermore, the change in the NT-proBNP concentration after 3 months was reportedly associated with subsequent mortality in hemodialysis patients.[2)] An increase in NT-proBNP over a 6-month period was also a risk factor for sudden death and cardiac death and was associated with mortality in hemodialysis patients with type 2 diabetes mellitus.[8)] Another recent report that monitored the monthly NT-proBNP levels showed that an increase in NT-proBNP measurements was associated with a risk of developing congestive heart failure within the next month in hemodialysis patients.[9)] Thus, preventing increases in the serum NT-proBNP level is likely to be very important for preventing cardiovascular events and reducing the mortality rate. In the present study, we investigated the change in the NT-proBNP level during a 12-month period, which was a relatively long observation period, and examined whether an increase in the NT-proBNP level was a risk factor associated with mortality during the next 24 months. In addition, we also investigated whether any factors were capable of predicting changes in the NT-proBNP level among hemodialysis patients.

Ⅱ. Materials and Methods

This study was performed as a regional sub-analysis for a prospective study known as Treatment for Renal Anemia on Prognosis in hemodialysis patients (TRAP), which was a 36-month prospective study examining the treatment of renal anemia at 60 dialysis facilities in Japan (n = 1095) that began in June 2007. The following patients were excluded from the present study: patients who received maintenance hemodialysis for <1 year; patients aged >75 years; patients with chronic inflammation, malignancy, hematological disorders, or severe liver dysfunction; and patients who received anti-inflammatory drugs or immunosuppressive agents. All the patients provided informed consent in accordance with the requirements of the Ethics Review Board (UMIN000000687). Among the nine areas (Tokyo, Saitama, Kyoto, Osaka, Hyogo, Kagawa, Fukuoka, Miyazaki, and Kumamoto) included in the TRAP study, measurements of the NT-proBNP level were only recommended in the Tokyo area (16 facilities, n = 122) for this sub-analysis. A total of 54 hemodialysis patients in the Tokyo area whose NT-proBNP levels were examined at the start of the study and again at 12 months thereafter were enrolled (Figure 1). We set the baseline at 12 months after the start of the TRAP study and investigated the patient outcome during the subsequent 24 months (Figure 2).

Figure 1. Disposition of the subjects.

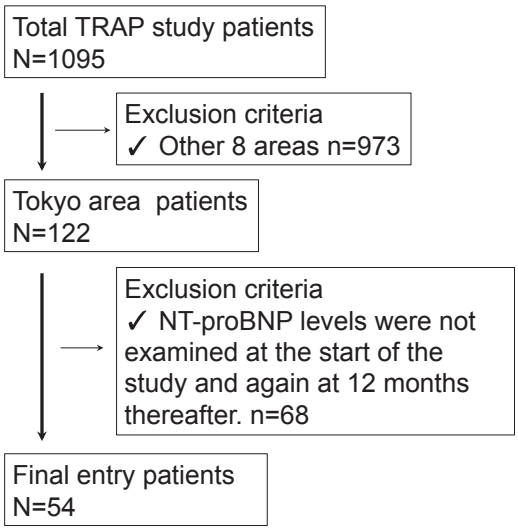
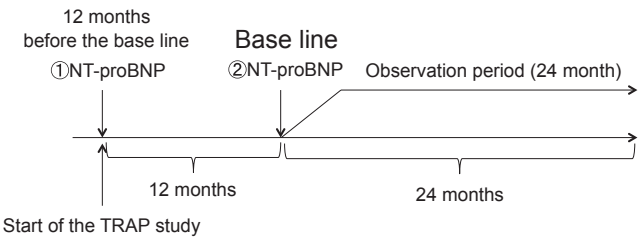


Figure 2. Baseline and observation period.



Blood pressure and heart rate were measured before hemodialysis therapy. A peripheral blood sample was obtained before hemodialysis on a Monday or a Tuesday. The serum NT-proBNP level in the pre-dialysis blood sample was measured using an electrochemiluminescence immunoassay on an Elecsys platform (Roche, Basel, Switzerland).

The NT-proBNP ratio (baseline versus 12 months before the baseline) was estimated. Clinical data including age, sex, duration of hemodialysis therapy, blood pressure, heart rate, use of drugs, and biological examinations at the time of both 12 months before baseline and at baseline were collected from the patients' records. The clinical endpoint was death from any cause. We then investigated the factors capable of predicting mortality. We compared the NT-proBNP ratio (baseline versus 12 months before baseline) and several clinical factors at 12 months before the baseline.

All the data were expressed as the mean ± S.D. Because of the skewed distribution of the NT-proBNP levels, the data were normalized using a logarithmic transformation for further statistical analysis. The Student t-test was used for comparisons between continuous variables. A univariate Cox proportional hazards model was used to identify predictors of overall survival. A simple regression analysis was used to examine the relationship between two continuous variables. All the statistical calculations were performed using the JMP 5.1 software program. P values of less than 0.05 were considered to denote statistical significance.

Ⅲ. Results

The patients' background characteristics at baseline are shown in Table 1. The mean age

Table 1. Background characteristics of the study participants at the time of baseline

Quantity	Alive (n=49)	Dead (n=5)	Total (n=54)	P value
Age (year)	61.2 ± 11.7	63.4 ± 8.8	61.4 ± 11.4	ns
Men / Women	28 / 21	4 / 1	32 / 22	ns
Duration of HD (month)	125.5 ± 114.6	116.2 ± 53.5	124.6 ± 110.1	ns
Primary Cause of ESKD, n (%)				
Chronic glomerulonephritis	24	2	26 (48.1)	
Diabetic Nephropathy	13	3	16 (29.6)	
Nephrosclerosis	3	0	3 (5.6)	
Polycystic kidney disease	3	0	3 (5.6)	
Unknown and others	6	0	6 (11.1)	
Drug usage, n (%)				
Beta-blocker	8	0	8 (14.8)	ns
Angiotensin converting enzyme inhibitor	6	0	6 (11.1)	ns
Angiotensin II receptor blocker	31	3	34 (63.0)	ns
Systolic blood pressure (mmHg)	149 ± 20	156 ± 14	149 ± 20	ns
Diastolic blood pressure (mmHg)	79 ± 14	76 ± 9	79 ± 14	ns
Heart rate (beat per minute)	74 ± 13	78 ± 11	75 ± 13	ns
Creatinine (mg/dL)	11.1 ± 2.6	10.2 ± 3.7	11.0 ± 2.7	ns
HS-CRP (mg/dL)	0.23 ± 0.38	0.80 ± 1.12	0.28 ± 0.50	0.013
Prealbumin (g/dL)	35.1 ± 8.4	28.2 ± 5.8	34.4 ± 8.4	ns
Hemoglobin (g/dL)	10.5 ± 1.1	10.7 ± 0.7	10.6 ± 1.1	ns
NT-proBNP (pg/mL)	5138 ± 4374	18620 ± 15796	6386 ± 7191	
Log [NT-ProBNP]	8.2 ± 0.9	9.3 ± 1.3	8.3 ± 1.0	0.014
NT-ProBNP ratio*	1.3 ± 0.7	6.6 ± 5.1	1.8 ± 2.2	<0.0001

HD: hemodialysis, ESKD: end-stage kidney disease, HS-CRP: high-sensitivity C-reactive protein, NT-proBNP: N-terminal pro-brain natriuretic peptide

*: Ratio of base line versus 12 months before base line

was 61.4 ± 11.4 years, and the mean duration of hemodialysis therapy was 124.6 ± 110.1 months. The table also includes the primary causes of end-stage kidney disease, drug usage, blood pressure, heart rate, and the results of the biochemistry tests.

The mean follow-up period was 1.8 ± 0.4 years. During the follow-up period, 5 deaths were recorded. The cause of death was infection in 3 patients, cardiovascular disease in one patient, and a tumor in one patient. A comparison of the cases that survived and those that died is shown in Table 1. HS-CRP, log [NT-proBNP], and the NT-proBNP ratio were significantly higher among the cases that died.

Table 2 shows a Cox proportional hazard analysis of covariates for the prediction of mortality. In the univariate analysis, predictors of mortality included a high serum level of high-sensitivity C-reactive protein (HS-CRP), a low serum level of prealbumin, and a high NT-proBNP ratio (P = 0.034, P = 0.020 and P < 0.001, respectively). The presence of diabetic nephropathy showed a tendency toward being a risk factor associated with mortality (P = 0.061). Table 3 shows the changes in the NT-proBNP level among the cases that died. Increases in NT-proBNP were observed in all the cases that died.

Table 4 shows the relationship between several clinical factors at 12 months before baseline and the NT-proBNP ratio. The NT-proBNP ratio was positively correlated with the heart rate (P = 0.0002). The NT-proBNP ratio could be predicted using the following formula:

Ratio of NT-proBNP = -3.86 + 0.075 x heart rate (beats/min).

According to the formula, the NT-proBNP ratio would not change (ratio = 1) when the heart rate was 65 beats/min. When the heart rate was 78 beats/min, the NT-proBNP ratio would double (ratio = 2).

Table 2. Cox proportional hazards analysis of the covariates for all cause of death (univariate analysis)

	Hazard Ratio (95% CI)	P value
Age (per year)	0.99 (0.91 - 1.10)	0.847
Duration of HD (per month)	1.00 (0.99 - 1.01)	0.771
Diabetic Nephropathy (Y)	2.67 (0.96 - 12.0)	0.061
Systolic blood pressure (per mmHg)	1.02 (0.97 - 1.06)	0.482
Diastolic blood pressure (per mmHg)	1.01 (0.94 - 1.08)	0.820
Heart rate (per beat per minute)	1.01 (0.94 - 1.08)	0.690
Creatinine (per mg/dL)	0.91 (0.60 - 1.34)	0.625
HS-CRP (per mg/dL)	4.59 (1.15 - 16.72)	0.034
Prealbumin (per g/dL)	0.83 (0.67 - 0.97)	0.020
Hemoglobin (per g/dL)	1.23 (0.52 - 2.17)	0.582
Log [NT-ProBNP] (per 1)	3.38 (0.97 - 14.82)	0.056
NT-ProBNP ratio* (per 1)	2.19 (1.42 - 4.86)	<0.001

HS-CRP: high-sensitivity C-reactive protein,
NT-proBNP: N-terminal pro-brain natriuretic peptide

*: Ratio of base line versus 12 months before base line

Table 3. Changes of NT-proBNP among dead cases

Case	NT-proBNP (pg/mL, 12 MB)	NT-proBNP (pg/mL, Base line)
1	1320	1500
2	1820	15600
3	3110	35000
4	3200	35000
5	5210	6000

12 MB: 12 months before base line

Table 4. The relationship between several factors of 12 months before the baseline and ratio of N-terminal pro-brain natriuretic peptide

Factors of 12 months before	r	P value
Age (year)	0.158	0.254
Duration of HD (month)	-0.130	0.347
Creatinine (mg/dL)	-0.011	0.935
HS-CRP(mg/dL)	0.030	0.827
Prealbumin (g/dL)	-0.166	0.229
Hemoglobin (g/dL)	-0.103	0.460
Systolic blood pressure (mmHg)	0.093	0.503
Diastolic blood pressure (mmHg)	0.064	0.646
Heart rate (beat per minute)	0.483	<0.001

HD: hemodialysis, HS-CRP: high-sensitivity C-reactive protein

Ⅳ. Discussion

Our results confirmed that an increase in the NT-proBNP level is a risk factor associated with mortality among hemodialysis patients. As a predictor of a change in the NT-proBNP level, the heart rate was found to be associated with the NT-proBNP ratio.

Natriuretic peptides, such as atrial natriuretic peptide (ANP) and BNP, are affected by the volume status, and their levels decrease during hemodialysis therapy. ANP has been reported to be more responsive to changes in intravascular volume because of its smaller molecular size and shorter half-life, whereas NT-proBNP has a larger molecular size and longer half-life, making it less affected by sudden changes in volume.[10] In previous studies examining the relationship between NT-proBNP and cardiac death or mortality, pre-dialysis serum samples, not post-dialysis samples, were used to estimate the NT-proBNP level.[8)9)] Consequently, we investigated the pre-dialysis NT-proBNP level in the present study.

NT-proBNP has been identified as a strong predictor of mortality,[11] and an increase in NT-proBNP is also a risk factor associated with mortality in hemodialysis patients.[2)8)9)] In our study, the NT-proBNP level tended to be a risk factor associated with mortality, but the trend was not significant ($P = 0.056$), possibly because of the relatively small number of participants in this study. An increase in NT-proBNP may have a greater influence on mortality than the NT-proBNP level itself. The previously reported observation periods for changes in NT-proBNP were 1, 3, and 6 months,[2)8)9)] whereas the period in our study was 12 months. We confirmed that the change in the NT-proBNP level over a 12-month period, which was a relatively long observation period, was also a risk factor associated with mortality.

Recently, a high HS-CRP level, a poor nutritional status, and an old age were reported to be correlated with an increased variability in the NT-proBNP level.[12] NT-proBNP has been shown to be lower in obese patients.[13] It has been hypothesized that adipocytes play a role in the clearance of natriuretic peptides.[14] In this study, we could not found an association between the NT-proBNP ratio and inflammation or nutritional factors, such as age or the creatinine, HS-CRP, or prealbumin level. Further large-scale studies are needed to confirm these relationships.

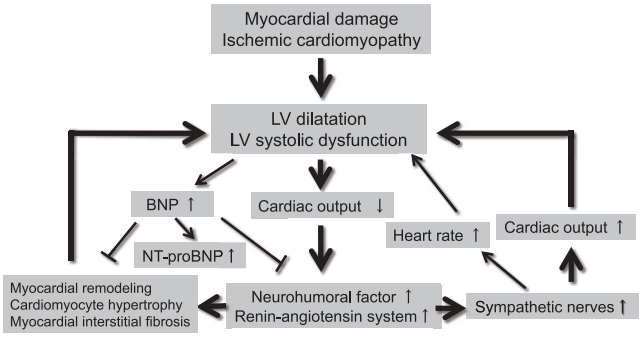
In our study, the heart rate was associated with the NT-proBNP ratio. An elevated resting heart rate was associated with an increased risk of incident heart failure in asymptomatic participants in the Multi-Ethnic Study of Atherosclerosis (MESA) trial. A higher heart rate was correlated with the development of regional and global left ventricular dysfunction independent of subclinical atherosclerosis and coronary heart disease.[15] An elevated heart rate is a known risk factor in the general population and in a variety of diseases and independently predicts early death.[16)17)18)] According to the NHANES study and the Framingham study, a pulse of greater than 84-85 beats/minute is the clinical cutoff for a risk of cardiovascular disease or mortality.[16)17)]Recently, an elevated heart rate has been reported to be a predictor of cardiovascular events in hemodialysis patients as well.[19)20)21)] Inoue et al. reported that receiver operating characteristic curves identified a heart rate cut-off level of ≥80 beats/minute for increased adverse outcomes in hemodialysis patients.[19] In the present study, the heart rate did not significantly affect mortality, but this outcome might have been caused by the relatively small number of subjects enrolled in this study. On the other hand, an increase of 100% NT-proBNP was associated with a higher risk of sudden death, cardiovascular events, and mortality.[7] The Japanese Heart Failure Society announced that early treatment is important when the NT-proBNP level is more than twice the previously measured value.[22] These two reports suggest that a change in the NT-proBNP level of more than double may have a significant impact. Interestingly, the NT-proBNP ratio was positively correlated with the heart rate at 12 months before the baseline. A two-fold NT-

proBNP ratio was associated with a heart rate of 78 beats/min. Thus, maintaining a heart rate of below 78 beats/min, which is almost the same as Inoue's cut-off level, might be important.

Based on Hase's "compensatory mechanism for progression of heart failure and its collapse" theory,[23] the possible correlation between the NT-proBNP level and the heart rate is shown in Figure 3. Myocardial damage, such as ischemic cardiomyopathy, results in left ventricular dilatation and systolic dysfunction. As a compensative reaction to left ventricular dysfunction, the sympathetic nervous system is activated by the renin-angiotensin system or other neurohumoral factors. These factors act to increase the venous return volume and to increase ventricular filling, thereby increasing the stroke volume (the Frank-Starling mechanism).[24] The activated sympathetic nervous system also directly increases cardiac output and the heart rate to compensate for the left ventricular dysfunction. In contrast, the renin-angiotensin system or other neurohumoral factors lead to myocardial remodeling, cardiomyocyte hypertrophy, and myocardial interstitial fibrosis, which adversely affect the left ventricular function.[23] BNP is secreted by cardiac myocytes in response to myocardial stretching and overloading and is an important regulator of blood volume homeostasis through its diuretic, natriuretic, and vasodilating actions by inhibiting renin and aldosterone.[25][26] BNP also appears to play a role in the prevention of cardiac fibrosis.[27][28][29] Therefore, the increase in the heart rate and the elevation in the BNP level belong to the same series of consequences. As myocardial remodeling affects cardiac dilatation, which develops slowly over a number of months,[24] the heart rate starts to increase earlier than the increase in NT-proBNP. Thus, the prevention of this malignant circle may be important.

The present study had several limitations. The small number of patients involved could reduce the study power. The effect of drugs such as beta-blockers, which affect heart rate, could not be estimated. Further large-scale study will be needed. Recently, the predialysis NT-proBNP level was reported to predict the magnitude of extracellular volume overload in hemodialysis patients.[28] However, we could not estimate the change in the extracellular volume status. We also could not investigate the previous history of cardiovascular disease, which is another predictor of mortality.

Figure 3. Compensatory mechanisms for progression of heart failure and its collapse.



V. Conclusion

We confirmed that an increase in NT-proBNP during a 12-month period, which was a relatively long observation period, was an independent risk factor associated with mortality among hemodialysis patients. We also found that heart rate was a predictor of a change in the NT-proBNP level. Maintaining a heart rate of less than 78 beats per minute might be important for preventing a change in the NT-proBNP level of more than double, which has been reported to be associated with adverse cardiovascular events.

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Disclosure

The authors state that they have no conflicts of interest (COI) to report.

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【原著】

血液透析患者における血清ヒト脳性ナトリウム利尿ペプチド前駆体Ｎ端フラグメント

大坪　茂[1)]　常喜　信彦[2)]　田中　友里[2)]　中西　健[3)]
倉賀野　隆裕[3)]　西條　公勝[4)]　長谷　弘記[2)]

要　旨

【目的】NT-proBNP 値の上昇は血液透析患者の生命予後に対する危険因子といわれている . 我々は 12 ヶ月の NT-proBNP の変化を予見する因子について調べた .

【方法】血液透析患者 54 名を対象とした . 研究開始 12 ヶ月後をベースラインとし , NT-proBNP の変化率（ベースラインとその 12 ヶ月前の比）を含む種々の因子とその後の 24 ヶ月の生命予後との関連を調べ , その NT-proBNP の変化率と研究開始時の各因子との関連を調べた .

【結果】単変量コックス比例ハザード分析にて NT-proBNP の変化率は生命予後の危険因子であった（Hazard Ratio 2.19, P < 0.001）. NT-proBNP の変化率は心拍数と正の相関を示した（P < 0.001）.

【結論】NT-proBNP の 12 ヶ月間での変化率上昇は透析患者の生命予後の危険因子であった . 心拍数は NT-proBNP の変化を予見した .

キーワード：血液透析 , 死亡率 , 心拍数 , ヒト脳性ナトリウム利尿ペプチド前駆体Ｎ端フラグメント