J Korean Med Sci 2009; 24 (Suppl 1): S63-8
ISSN 1011-8934
DOI: 10.3346/jkms.2009.24.S1.S63

N-terminal Pro-Brain Natriuretic Peptide Levels Predict Left Ventricular Systolic Function in Patients with Chronic Kidney Disease

N-terminal pro-brain natriuretic peptide (NT-proBNP) can be a useful marker for left ventricular (LV) dysfunction in patients without kidney disease. This study was conducted to clarify the relationship between NT-proBNP and LV systolic function in patients with decreased renal function. We studied 256 chronic kidney disease (CKD) patients, patients on dialysis were excluded. The median glomerular filtration rate was 24 (13-36) mL/min/1.73 m^2 and the median NT-proBNP was 4,849 (1,310-19,009) pg/mL. The prevalence of LV systolic dysfunction increased from the lower to the upper NT-proBNP quartiles (I, 17%; II, 34%; III, 61%; and IV, 72%; $p<0.001$ for trend). The NT-proBNP quartile was an independent predictor of LV systolic dysfunction after adjustment for renal function, compared with quartile I: II, odds ratio (OR) 3.99 (95% confidence interval [CI],1.34-11.93); III, OR 11.28 (95% CI, 3.74-33.95); and IV, OR 36.97 (95% CI, 11.47-119.1). Area under the curve and optimum cut points for NT-proBNP to detect LV systolic dysfunction were 0.781 and 2,165 pg/mL in CKD stage 3, 0.812 and 4,740 pg/mL in CKD stage 4, and 0.745 and 15,892 pg/mL in CKD stage 5. The NT-proBNP level was a predictor of LV systolic dysfunction in CKD patients. Optimum cut points should be stratified according to renal function.

Key Words : *Biological Markers; Kidney Failure, Chronic; Ventricular Dysfunction, Left; Pro-brain Natriuretic Peptide (1-76)*

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Received : 27 August 2008
Accepted : 17 December 2008

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*This work was supported by a grant from IN-SUNG Foundation for Medical Research and Samsung Medical Center.

INTRODUCTION

It is estimated that more than 10% of adults have chronic kidney disease (CKD), and its prevalence is gradually increasing (1). Patients with chronic kidney disease are at increased risk of cardiovascular death (2). Left ventricular (LV) systolic dysfunction is a common terminal pathway for a variety of heart diseases. The presence of LV systolic dysfunction is associated with high morbidity and mortality in CKD patients (3). However, LV systolic dysfunction is difficult to identify based solely on the clinical history and physical examination, because neither is specific nor sensitive (4, 5). Although echocardiography is the current "gold standard" for evaluation of cardiac dysfunction (3), it is expensive and not always readily available.

Recently, brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) have been extensively studied as useful biochemical markers of ventricular dysfunction and heart failure in the general population (5-8). The kidney appears to play an important role in the clearance of NT-proBNP. Several studies have demonstrated that impaired renal function increases NT-proBNP levels, independent of ventricular function (9, 10). Therefore, diagnostic value of NT-proBNP to predict LV systolic function in patients with significant renal impairment remains unclear. Moreover, potential cut points of NT-proBNP to detect LV systolic dysfunction in patients with CKD has not been systematically evaluated. For these reasons, we undertook this study to evaluate whether NT-proBNP levels could predict ventricular dysfunction in patients with established CKD.

MATERIALS AND METHODS

Patients

We enrolled retrospectively adult patients with CKD who visited the outpatient clinic of the Department of Nephrology or the emergency room between March 2003 and March 2005 on whom we performed both NT-proBNP measurement and echocardiography. We excluded patients undergoing dialysis or those with a glomerular filtration rate (GFR) greater 60 mL/min/1.73 m^2. A total of 274 patients were identified. We then excluded 18 patients who were finally diagnosed as having pulmonary diseases such as pulmonary thromboembolism or pneumonia. This left a final set of 256 patients to be analyzed. The causes of CKD were diabetic nephropathy (155 patients), hypertensive nephrosclerosis (34 patients), chronic

glomerulonephritis (25 patients), autosomal dominant polycystic kidney disease (five patients), other causes (four patients) and unknown causes (33 patients). 78 patients were enrolled in outpatient clinics and others were enrolled in emergency room.

Clinical variables

Patients' demographic and clinical information were obtained by chart review. A diagnosis of diabetes, hypertension, and coronary artery disease (CAD) were included if they were identified in the patient's history and/or by physical examination. CAD was defined as documented myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention. The GFR was estimated using the abbreviated Modification of Diet in Renal Disease formula (1). Each estimated GFR was categorized into one of three groups as less than 15 mL/min/1.73 m^2 (CKD stage 5), 15-29 mL/min/1.73 m^2 (CKD stage 4), and 30-59 mL/min/1.73 m^2 (CKD stage 3) (1).

Echocardiographic measurement and definition

Echocardiography was performed as per our standard laboratory protocol by one of five expert sonographers. Findings were analyzed to quantify LV ejection fraction (EF) and LV mass. LV mass was determined by using the formula of Devereux et al. (11) which was adjusted for height. Left ventricular hypertrophy (LVH) was considered to be present when the LV mass index was greater than two standard deviations above the mean of the respective gender control group. The EF was calculated by the Simpson method, using end-diastolic volume and end-systolic volume measurements. LV systolic dysfunction was defined as an LV EF of 50% or less.

Assay for NT-proBNP

Blood samples were drawn routinely in lithium heparin tubes and centrifuged at 1,000 g for 12 min. The plasma was used for measurement of NT-proBNP using a commercially available immunoassay (Elecsys proBNP; Roche Diagnostic Corp, Indianapolis, IN, U.S.A.) on an Elecsys 1,010 analyzer according to the manufacturer's directions. The measurable range of the NT-proBNP assay was up to 35,000 pg/mL.

Statistical analysis

Data for continuous variables were expressed as median and interquartile ranges. Categorical variables were expressed as absolute numbers and percentages. Comparisons between three or more data groups were analyzed by a nonparametric (Kruskal-Wallis) test for continuous variables and by a likelihood ratio test for trends for categorical variables. To assess the independent contribution to LV systolic dysfunction, we used logistic regression. A p value of less than 0.05 was considered to be statistically significant. Separate receiver operating characteristic (ROC) curves were generated for NT-proBNP and detection of LV systolic dysfunction, as a function of GFR categories. All statistical analyses for this study were conduct-

Table 1. Clinical characteristics and echocardiographic findings according to NT-proBNP quartiles

Variables	Quartile I (40-1,303 pg/mL)	Quartile II (1,331-4,773 pg/mL)	Quartile III (4,925-18,392 pg/mL)	Quartile IV (19,215-35,000 pg/mL)	*p*
No of Patients	64	64	64	64	–
Age (yr)	65 (58-73)	67 (54-77)	67 (61-73)	63 (53-74)	NS
Men	39 (61%)	40 (63%)	40 (63%)	30 (47%)	NS
*NYHA class O or I/II/III/IV	42/5/10/3	31/11/15/2	20/7/18/15	14/8/14/18	<0.001
*Orthopnea (yes/no)	9/52	8/52	17/40	29/30	<0.001
*LE edema (yes/no)	10/52	15/44	25/37	37/24	<0.001
Diabetes	34 (53%)	31 (48%)	36 (56%)	46 (72%)	0.004
Hypertension	45 (70%)	43 (67%)	48 (75%)	49 (77%)	0.036
Coronary artery disease	9 (14%)	21 (33%)	26 (41%)	20 (31%)	<0.001
Hemoglobin (g/dL)	10.3 (9.0-12.0)	9.6 (8.4-11.2)	10.8 (9.3-12.4)	9.3 (8.4-10.7)	0.012
GFR (mL/min/1.73 m^2)	30 (20-43)	25 (16-37)	22 (13-38)	18 (9-28)	<0.001
CKD stage 3/4/5	32/21/11	23/27/14	21/23/20	11/22/31	<0.001
LV MI (gm/m^2)	148 (118-178)	146 (114-175)	169 (144-202)	181 (154-221)	<0.001
LV EF (%)	62 (55-68)	58 (44-67)	45 (30-58)	40 (34-52)	<0.001
*LVH (yes/no)	34/20	41/19	53/7	52/9	<0.001
LV EF <40%	2 (3%)	14 (22%)	27 (42%)	33 (52%)	<0.001
LV EF <50%	11 (17%)	22 (34%)	39 (61%)	46 (72%)	<0.001

Values expressed as median (interquartile range). Categorical data expressed as number (percent).
*We could not assess information regarding these variables in some patients (less than 10% of the study patients). Thus, the sums of numbers given do not equal 256.
NYHA, New York Heart Association; LE, lower extremity; GFR, glomerular filtration rate; LV MI, left ventricular mass index; LV EF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NT- proBNP, N-terminal pro-brain natriuretic peptide.

ed with SPSS 11.0 for Windows.

RESULTS

The demographics of the study patients were as follows. The median age was 66 (58-74) yr. There were 149 men and 107 women. The most prominent symptoms were shortness of breath in 111 patients, chest discomfort in 45 patients, peripheral edema in 18 patients, and other symptoms in 59 patients. Twenty-three patients were asymptomatic. The median GFR was 24 (13-36) mL/min/1.73 m^2 and the median NT-proBNP level was 4,849 (1,310-19,009) pg/mL. LVH was present in 77% of the patients and 118 (46%) had LV systolic dysfunction. Clinical and echocardiographic findings stratified by NT-proBNP quartiles are listed in Table 1. Patients in the upper NT-proBNP quartiles showed higher New York Heart Association function classes. Orthopnea and lower extremity edema were observed more often in patients in upper NT-proBNP quartiles. Diabetes, hypertension, and CAD were also more prevalent in the upper NT-proBNP quartiles. Median estimated GFR and median LV EF decreased from the lower to the upper NT-proBNP quartiles. The prevalence of LV systolic dysfunction increased from 17% in the lowest quartile to 72% in the highest quartile.

We classified patients by CKD stage, with 87 (34%) patients with CKD stage 3, 93 (36%) with CKD stage 4, and 76 (30%) with CKD stage 5. Table 2 shows clinical and echocardiographic findings according to CKD stages. Orthopnea and lower extremity edema were observed more often in patients with advanced stage of CKD.

Fig. 1 shows median NT-proBNP levels according to LV systolic function and CKD stage. The median NT-proBNP level increased progressively with lower LV EF in each CKD stages (all $p<0.001$ for trend). Also the median NT-proBNP level increased from CKD stage 3 to stage 5 in each LV EF groups (all $p<0.001$ for trend). Of note is that CKD stage 5 patients with normal LV systolic function had NT-proBNP levels similar to those in CKD stage 3 patients with LV EF of less than 40% (8,859 [1,672-21,831] pg/mL vs. 8,026 [2,605-17,994] pg/mL).

Multiple logistic regression analyses were performed to determine whether the NT-proBNP level could independently predict the presence of LV systolic dysfunction. The NT-proBNP quartile was found to be an independent predictor of LV systolic dysfunction after adjustment for age, gender, CAD, diabetes, hypertension, GFR, hemoglobin levels, and LVH. The odds ratio of having LV systolic dysfunction increased

Table 2. Clinical characteristics and echocardiographic findings according to CKD stages

Variables	CKD stage 3	CKD stage 4	CKD stage 5	*p*
No of Patients	87	93	76	
*NYHA class				
O or I/II/III/IV	50/10/20/7	25/6/24/15	32/15/13/16	0.005
*Orthopnea (yes/no)	14/73	22/53	27/48	0.001
*LE edema (yes/no)	19/68	29/56	39/33	0.001
*LVH (yes/no)	51/21	64/23	65/11	0.001
LV EF <50%	45 (52%)	46 (50%)	27 (36%)	0.042

Data expressed as number (percent).
*We could not assess information regarding these variables in some patients. Thus, the sums of numbers given do not equal 256.
NYHA, New York Heart Association; LE, lower extremity; LVH, left ventricular hypertrophy; LV EF, left ventricular ejection fraction.

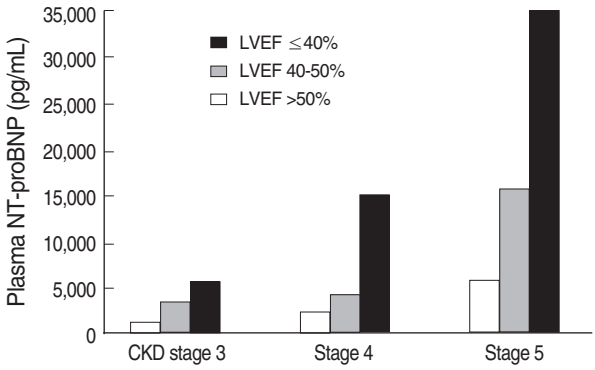

Fig. 1. Median NT-proBNP level according to left ventricular systolic function and CKD stage ($p<0.01$ for both inter-CKD stages and inter-LV EF groups).

Table 3. Multiple logistic regression models-association between NT-proBNP quartiles and LV systolic function

	LV EF <50%		LV EF <40%	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
NT-proBNP				
Quartile I	1		1	
Quartile II	3.99 (1.34-11.93)	0.013	28.08 (2.63-299.1)	0.006
Quartile III	11.28 (3.74-33.95)	<0.001	56.39 (5.58-569.5)	0.001
Quartile IV	36.97 (11.47-119.1)	<0.001	256.6 (22.57-2915)	<0.001

These models also included age, gender, coronary artery disease, diabetes, hypertension, glomerular filtration rate, hemoglobin, and left ventricular hypertrophy.
LV EF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide.

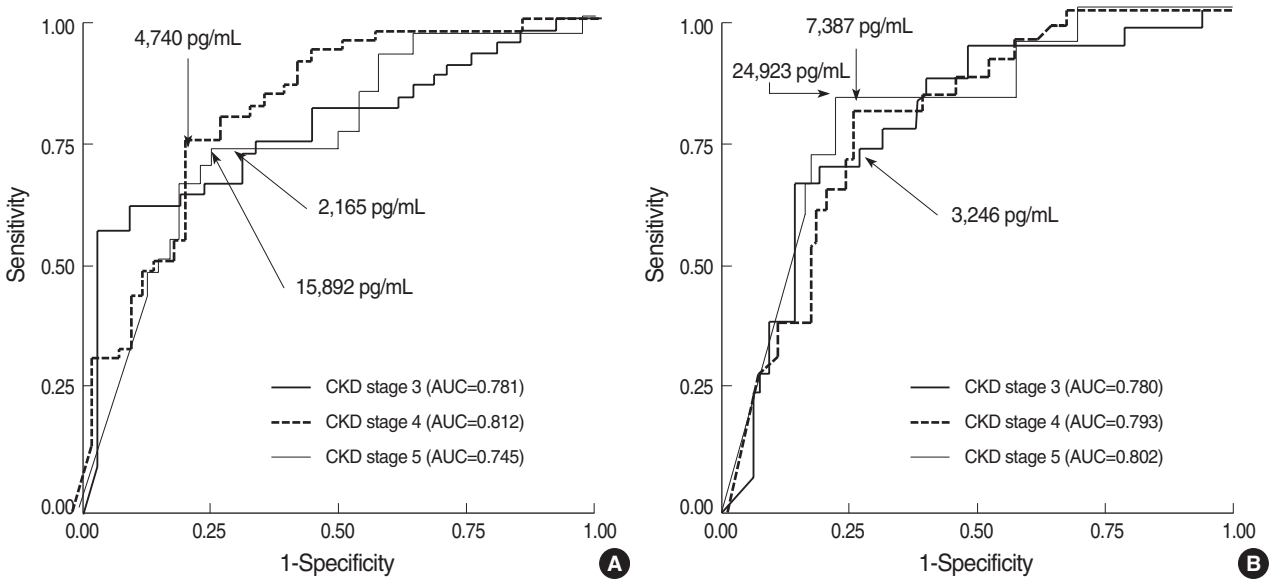

Fig. 2. Receiver operating characteristic curves for NT-proBNP to detect LV EF ≤50% (A) and LV EF ≤40% (B) in each stages of CKD.

progressively in the higher NT-proBNP quartiles. Patients in the highest quartile had nearly 37-fold increased odds of having LV systolic dysfunction, compared with those in the lowest quartile (odds ratio 36.97; 95% CI, 11.47 to 119.1). The NT-proBNP quartile was also an independent predictor of having an LV EF less than 40%.

ROC curves for NT-proBNP to detect LV systolic dysfunction (LV EF ≤50%), and for each of the CKD stages, are presented in Fig. 2A. AUC and optimum cut points were 0.781 and 2,165 pg/mL, 0.812 and 4,740 pg/mL, and 0.745 and 15,892 pg/mL in patients with CKD stage 3, 4, and 5. Using these levels, the sensitivity and specificity of NT-proBNP were 73% and 69%, 76% and 77%, and 74% and 74% in CKD stage 3, 4, and 5, respectively. AUC to detect severe LV systolic dysfunction (LV EF ≤40%) were 0.780, 0.793, and 0.802 for CKD stage 3, 4, and 5, respectively (Fig. 2B). Optimum cut points for NT-proBNP increased progressively with CKD stage.

DISCUSSION

This study demonstrates that NT-proBNP was an independent predictor of LV systolic dysfunction in patients with established CKD. Although NT-proBNP level was increased with decreasing GFR, the NT-proBNP level was negatively associated with LV EF independent of renal dysfunction. Optimum cut points of NT-proBNP to detect LV systolic dysfunction were much higher in CKD patients than those reported in the general population and these were increased progressively with lower renal function. These results suggest that even in patients with advanced renal dysfunction, the measurement of NT-proBNP level might be of benefit in predicting LV systolic function in the setting of suspected heart failure and that the NT-proBNP level should be interpreted along with values for renal function in order to predict LV systolic dysfunction. If cut points without adjustment for renal function are applied, the usefulness of NT-proBNP levels is limited in CKD patients.

The diagnostic and prognostic roles of NT-proBNP have been well established in a variety of cardiac diseases (9, 10, 12-15). Most investigators have excluded CKD patients from their studies because of potentially elevated levels of the peptide (9, 10, 12-15). However, an easily measurable biomarker for cardiac disease is sorely needed in CKD patients, because symptoms mimicking congestive heart failure occur very often among them (3). Our study suggests that NT-proBNP measurement might be used as a screening tool in CKD patients with clinically suspected LV systolic dysfunction. Compared with patients in the lowest NT-proBNP quartile, patients in the upper quartiles had an increased probability of LV systolic dysfunction, based on multivariate analysis.

Previous studies investigating the clinical implications of NT-proBNP measurement in CKD patients showed that NT-proBNP quartile were associated with LVH and coronary artery disease in stable pre-ESRD patients (16-19). In our current study, the prevalence of LVH increased in the higher NT-proBNP quartiles. However, after adjustment for the GFR, levels of NT-proBNP alone could not predict the presence of LVH (data not shown). A thickened LV wall might lead to an increased secretion of NT-proBNP in CKD patients, just as in subjects without kidney disease (11). We presume that the effect of LVH on the NT-proBNP level was much smaller than the effect of impaired renal function or LV systolic dysfunc-

tion. Accordingly, NT-proBNP was not an independent predictor of LVH in our patients with a high prevalence of LV systolic dysfunction and advanced renal dysfunction. Previous studies showed lower prevalence of LV systolic function than our study and the relation between LV systolic function and NT-proBNP levels were not evaluated systemically. Although a few studies have shown that NT-proBNP level was associated with LV systolic function in CKD patients, independent association were not evaluated (20, 21).

It is well established that impaired renal function is associated with an elevated NT-proBNP level (9, 10, 14, 18). The NT-proBNP level is likely to increase corresponding to the severity of renal dysfunction by several possible mechanisms. Decreased renal clearance may play a role, at least in part (22). Concomitant anemia and cardiac overload may contribute to an increase in the NT-proBNP level in CKD patients, in the same manner as for the BNP level (22). Elevated NT-proBNP may also reflect silent myocardial infarction, LVH or diastolic dysfunction (18, 23).

The high prevalence of LV dysfunction seen in our study is noteworthy. There were 46% of patients with LV systolic dysfunction and 77% of patients with LVH. Higher prevalence of LV systolic dysfunction than in previous studies on CKD patients (16-18) could be explained that we included patients who need emergent treatment and most patients were symptomatic.

Several limitations apply to this study. First, we did not consider volume status or silent myocardial ischemia. Both might be associated with NT-proBNP levels in CKD patients. However, it is difficult to evaluate the exact volume status or assess silent myocardial ischemia based solely on clinical findings. Second, the NT-proBNP assay used in the study has an upper limit of 35,000 pg/mL. 14% of our study patients had a NT-proBNP level equal or greater to this. Therefore, we could not analyze direct correlations of the NT-proBNP level with GFR or LVEF. Instead, we stratified by quartiles to analyze the relationship between NT-proBNP levels and LV systolic function. Third, the fact that our study patients were relatively old limits the generalizability of our finding in the whole CKD patients. Fourth, GFRs estimated using the abbreviated MDRD study equation were used to classify CKD stages. Although, the MDRD study equation has been used widely in large epidemiologic studies and in clinical practice, it has not been validated for the Korean population.

In summary, although the NT-proBNP level is increased in the majority of patients with renal dysfunction, higher NT-proBNP levels were associated with a higher prevalence of LV systolic dysfunction, independent of renal function. The measurement of NT-proBNP levels might be of benefit in the prediction of LV systolic function in CKD patients with suspected congestive heart failure. However, renal function must be taken into consideration when NT-proBNP measurement is used as a diagnostic tool. A prospective study is needed to determine the diagnostic value and optimal cut-off levels for NT-proBNP for predicting LV dysfunction in CKD patients.

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