Pak. J. Biochem. Mol. Biol. 2010; 43(2): 99-104

Evaluation of NT pro BNP of diagnostic significance in patients with chronic kidney diseases

Jawaid Altaf Baig[1], Junaid Mahmood Alam[2], Maqsood Ali Ansari[3], Amna Hussain[2], Suad Naheed[4], Rabia Shaheen[2] and Ishrat Sultana[2]*

[1]Department of Biochemistry, Liaquat National Hospital and Medical College, and Biochemistry Laboratory Services[2], Karachi, Pakistan
[3]Department of Genetics, University of Karachi, Pakistan
[4]HEJ-Research Institute of Chemistry, International centre for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan

Abstract: Amino-terminal pro-B type natriuretic peptide (NT-proBNP) is a known biomarkers of myocardial dysfunction and offers the potential for early detection and management of cardiac disease. However suggestions were made that its diagnostic utility should be extended chronic kidney disease (CKD) patients that are devoid any cardiovascular dysfunction symptoms. The goal of present study was to further evaluate the relationship between CKD and NT-BNP concentration in a prospective cohort of patients with varying levels of renal function including End Stage Renal Disease (ESRD). Stable adult patients of both gender (n = 89) with CKD (study period May 2006 to August 2008) were included in the study who had been on hemodialysis (HD). Echocardiography (trans-thoracic) measurement was performed for left ventricular ejection fraction (LVEF) and dysfunction which was defined as ejection fraction (EF <50%. Other parameters such as mean arterial pressure (MAP), NT proBNP and biochemical parameters were measured using standard procedures. The results presented an association of NT-proBNP levels with CKD patients which were without a definite left ventricle dysfunction (LVD). Furthermore, NT pro-BNP correlated significantly with a higher protein to creatinine ratio and blood urea nitrogen ($P < 0.01$) suggesting that onset and presence of CKD influenced the levels of natriuretic peptides. Studies regarding assessment of NT pro BNP in CKD patients, such as ours, provided evidence that adverse renal function and natriuretic peptides, especially NT-proBNP are correlated with each other. However, additional prospective studies are required to validate and better define this relationship.

Keywords: Natriuretic peptides, amino-terminal pro-B type natriuretic peptide (NT-proBNP), Left Ventricle Dysfunction (LVD).
Received: February 20, 2010 **Accepted:** May 4, 2010
***Author for Correspondence:** arshadpcsir@yahoo.com

INTRODUCTION

It is well documented that patients with chronic kidney disease (CKD) are at increased risk of cardiovascular disease. Natriuretic peptides (NPs), especially amino-terminal pro-B type natriuretic peptide (NT-proBNP) and BNP biomarkers of myocardial dysfunction, offers the potential for early detection and management of cardiac disease, mostly in emergency department and Intensive Care units[1-4]. It was researched and ultimately suggested that screening utility could be extended to CKD patients devoid any symptoms relating to cardiovascular disease[5]. However, the affects of CKD on blood levels of NT-proBNP in clinical practice, continues to be questioned[5]. Dependence of plasma NT-BNP on glomerular filtration rate (GFR) has been reported among patients with and without heart failure (HF) (5-9). But it was argued that this relationship may not be independent of cardiac or volume-related factors[10,11]. It was documented that patients with CKD, including those with stage 5, have one of the highest CV risk scores[9,12-15]. In this type of specific population, the clinical benefit of NT-pro BNP measurements has not been yet thoroughly researched and established to the fact that patients with CKD have significantly increased BNP and NT-proBNP levels[9,12-14].

Thus, to contribute and established the notion that CKD have influence on NT- pro-BNP levels and thus advocates its clinical value, NT-BNP measurements need to be explored within the context of renal function only. The goal of present study was to further evaluate the relationship between CKD and NT-BNP concentration in a prospective cohort of patients with varying levels of renal function including End Stage Renal Disease (ESRD).

MATERIALS AND METHODS

Patients and procedures

We studied 89 stable adult patients with CKD who had been on hemodialysis (HD) for at least 15 weeks prior to the present prospective study. The study was conducted during the period May 2006 to August 2008. For most of procedures, protocols of David *et al.*, 2008[9] was followed for proper management of the analyses. All patients were clinically stable and those with acute cardiac disease and/or acute cardiac failure were excluded from the study. Major causes of CKD leading to renal failure are shown in Table 1. Blood pressure was measured and mean arterial pressure (MAP) was calculated accordingly. All measurements were performed twice and the means were used for analysis. According to grading described earlier[9], the presence

of oedema was assessed clinically and determined according to the following scheme:

Grade I—absence of oedema, grade II—mild oedema,, grade III—moderate oedema and gradeIV—severe oedema (Table 2). Clinical data were obtained from patients' records. Echocardiography (trans-thoracic) measurement was performed in all patients and left ventricular ejection fraction (LVEF) was measured according to established method[16]. This procedure has been performed twice and the mean EF value was used for analysis. To avoid bias, the investigators who performed the echocardiography were not informed about the volume status and NT-pro-BNP level of patients examined. Left ventricular dysfunction (LVD) was defined as LVEF <50%.

Table 1: Etiology of chronic kidney disease leading to terminal renal failure.

Condition:	Pt *n*	Percentage onset
Glomerulonephritis	29	32.60
Nephrosclerosis	8	8.90
IgA nephropathy	4	4.50
Others	13	14.60
Hypertensive nephropathy	15	16.80
Analgetic nephropathy	5	5.60
Diabetic nephropathy	14	15.70
Haemolytic uremic syndrome	1	1.12

Table 2: Four-point scale of the clinical presence of edema.

Grade	Description	*n*	%
I	Absence, of any oedema	41	46.06
II	Mild, bilateral ankle oedema	25	28.08
III	Moderate, ankel and lower leg oedema	22	24.71
IV	Severe, with generalised oedema	01	1.12

Biochemical measurements

Blood samples from all patients were collected during the post-dialysis periods to avoid discrimination in volume status. After centrifugation (2000 rp/min, 5 min), samples were stored at −20°C until further analysis. NT proBNP was measured using a commercially available electro-chemoluminescence immunoassay (Roche, Basel, Switzerland) that was performed on a Roche Elecsys 2010 analytical system. All other biochemical parameters, including BUN, creatinine, calcium phosphorus, albumin, C-reactive protein (CRP), were measured with routine laboratory methods on Hitachi 912 Chemistry analyzer (Roche) and electrolytes (Na, K, Cl, HCO3) on NOVA Crt 4 (Nova Biomedical, USA). Results were expressed as mean±SD.

Statistical analysis

SPSS statistic software 13.0 (Lead Technologies Inc., Chicago, USA) were used for statistical analysis. Data are expressed as mean±SD. Subgroups were compared using one-way ANOVA. To compare NT-proBNP levels between groups Pearson's correlation analysis was applied. Correlation analysis between different variables was done by using Pearson's correlation coefficient. Independent variables associated with LVD, i.e. an EF<50%, multivariate regression analysis was performed using variables which were correlated with EF in the univariate analysis, e.g. NT-proBNP, age, haemoglobin, haematocrit, left ventricular hypertrophy (LVH).

Table 3: Clinical characteristics and laboratory data of patients categorized in two groups according to left ventricular ejection fraction.

	EF < 50% left ventricular dysfunction (LVD)		**EF > 50% Normal Left Ventricular function**	
n	*41*	*P value*	*48*	*P value*
Age [years]	68 ± 4.4	0.8	55 ± 2.4	0.99
Weight [kg]	64.2 ± 5.2	0.809	78.1 ± 2.5	0.432
EF [%]	47.5 ± 1.6	0.817	64.1 ± 2.1	0.476
NT-proBNP [ng/l] post-HD	24,216 ± 6,111	<0.0001*	18,112 ± 1185	0.005*
P:C ratio	2.9 ± 0.01	< 0.01*	2.1 ± 0.003	< 0.001*
BUN (mg/dl)	59.72 ± 3.41	< 0.01*	38.71 ± 2.14	< 0.01*
MAP pre-dialysis	90.1 ± 2.5	0.330	92.1 ± 2.0	0.902
Post-dialysis	81.2 ± 1.7	0.123	80.2 ± 1.4	0.788
Hb [g/dl]	12.0 ± 0.5	0.612	13.2 ± 0.31	0.845
Hct	0.35 ± 0.02	0.529	0.34 ± 0.01	1.0
CRP [mg/l]	9.2 ± 2.3	0.421	10.0 ± 1.8	1.0
Albumin [g/l]	39.2± 1.1	0.873	36.4 ± 1.4	0.892

NTproBNP - N - terminal pro-B-type natriuretic peptide; BP - blood pressure; MAP – Mean arterial pressure; P:C – protein to creatinine ratio; Hb - haemoglobin; Hct - haematocrit; CRP - C-reactive proteine; ($p > 0.05$); EF - ejection fraction

RESULTS

Around 200 eligible patients were screened for present prospective study and only 89 met criteria for CKD and negative for CHF. Etiology of CKD is summarized in table 1. Four point scale of edema as per description stated earlier[9] is in table 2, which shows presence of edema in more than 50% patients. Only one patient was related to status of ESRD with increased level of protein to creatinine ratio of 3.0, BUN 64 mg/dl (pre) and 38 mg/dl (post-dialysis) and NT-proBNP 28,129 ng/l. In overall group of patients, increasing severity of underlying comparatively low ejection fraction or a possible congestive heart failure was found associated with a higher NT pro-BNP (P<0.05), but not as significant as was assumed (Table 3). In addition, there was a significant inverse association between NT pro-BNP and low EF (< 50%) (P<0.001), with higher NT pro-BNP levels observed in those with lower < 50% EF. As regard the biochemical parameters, NT pro-BNP correlated significantly with a higher protein to creatinine ratio and blood urea nitrogen ($P < 0.01$) suggesting that onset and presence of CKD influenced the levels of natriuretic peptides. MAP, both pre and post-dialysis, Hb, Hct, CRP and albumin shows no significant correlation with patients showing either lower or higher than 50% EF (depicting LVD or normal cardiac functions respectively) and NT-proBNP. The results of present study clearly indicates that the NT pro-BNP represented itself as an independent diagnostic factor which may be useful clinically to evaluate onset or severity of patients of CKD and renal failure.

DISCUSSION

B type natriuretic peptide (BNP) belongs to a family of natriuretic proteins (NP), the physiological function of which is to maintain sodium homeostasis and protection of the cardiovascular system from volume overload[1,8]. NT-proBNP represent cleavage products of the precursor pre-pro BNP which is synthesized by ventricular myocytes in response to physiological signals such as stretching of the ventricular wall, changes in systemic blood pressure, sodium levels or extracellular volume[8]. The action of BNP is mediated through metabolism by specific natriuretic peptide receptors of kidney, lung, liver and along the vascular endothelium, while the NT BNP is mainly cleared by the kidneys[8,17]

In the present study, we postulated and then investigated whether the natriuretic peptide NT-proBNP may be of clinical value in the assessment of CKD in patients with or without underlying LVD or vice versa, since its diagnostic potential in CHF has been extensively studied in patients with normal kidney function[1–3,6,9]. We clearly noted elevated NT-proBNP levels in our CKD patients; but slightly higher in patients with EF<50%. Our results are in agreement with earlier reported studies showing increased levels of natriuretic peptides as a result of reduced renal excretion and chronic volume overload in CKD patients without LVD[9,12,21-24]. However as pointed out and suggested earlier[9] that a recommended specific reference values of NT-proBNP, to be used routinely as a diagnostic tool, is not available yet to separate LVD from over-hydration in CKD patients. The researcher also recommended that with respect to the previously demonstrated impact of NT-proBNP as a predictor of mortality in CKD patients[25], the need to define an NT-proBNP cut-off value for such use in clinical practice is mandatory. It was extensively argued by some authors[9] that studying the temporary changes of NT-proBNP levels as a result of HD-related ultrafiltration was not the target, since this is not helpful in the diagnosis of LVD in patients requiring HD therapy[26]. The assessment of NT proBNP levels, therefore, was done in post-dialytic period in order to minimise the chance of fluid overload and ideally assess levels when patients reached their 'dry' weight. Moreover, NT-proBNP level was more quickly manifested by candidate variables, most notably GFR, or more commonly the kidney functions, which explained more than one third of the variance[5]. A correlation of NP levels with age, especially NT-proBNP, has been reported in both Western[27,28] and Asian populations[5,29]. A study reported age as a dependent variable correlated with plasma NP levels in univariate analysis but lacked independent predictive value[5]. The researchers argued that this is not unexpected in a CKD cohort study where LV hypertrophy, a variable highly correlated with age, is known. It was noted and reported that CKD and consequent end-stage renal failure are going to reach epidemic proportions worldwide over the next decade[5,15]. Thus, it was pointed out that an increasing number of CKD patients will require early initiation of management protocols and screening for co-morbidity, such as cardiac problems[5]. For this purpose considerable attention has been given to the issue of how to differentially interpret BNP in the presence or absence of CHF and within the context of renal function only. However, it remains a considerable important factor but remains incompletely resolved

from a clinical perspective[5,28]. Currently, usual clinical decisions for CHF, which incorporate BNP results, are made without evaluating or assessing renal function status of patients.

A study of a cohort of 3916 patients with heart failure suggested that BNP and NT-pro BNP were independent markers correlating strongly with outcomes of CHF including: mortality, morbidity and hospitalization[30]. Other factors that have correlated with BNP levels included age, New York Heart Association (NYHA) class, ventricular function, body mass index, cardiac arrhythmia, ischemia, diurtetics, bilirubin, creatinine, and C reactive protein[8]. In another study of 213 subjects, it was demonstrated that as renal function declined, BNP levels increased, especially among the subset of patients with ventricular hypertrophy[31]. Similarly, another group of researchers found that among 389 patients, with and without de-compensated heart failure, those with GFR greater than 60 mL/min/1.73m2 had lower BNP levels than patients whose GFR less than 60 mL/min/1.73m2[32]. BNP levels, when assessed in dialysis patients, it was noted that BNP levels were predictive of presence of left ventricular dysfunction, cardiac events and survival in the presence of end stage renal disease, thus further concluding that BNP levels may provide information regarding overall status of renal function[22]. A more comprehensive study was conducted in which patients were recruited to cover a variable range of renal function including patients on hemodialysis, with functional renal allograft and patients assessed by creatinine clearance measurements. Patients were further evaluated for heart function by echocardiography for cardiac hypertrophy, dilatation, systolic and/or diastolic dysfunction, pharmacological treatment and blood chemistry[33]. The authors concluded that the range of renal function factors represented in the population studied, it was the factor-GFR, which superseded ventricular function as the more important determinant deciding serum BNP levels[8,34]. It was also further noted that in addition to GFR, hypoalbuminemia, anemia, use of beta blockers and age were significant confounders of serum BNP levels, as has also been reported in earlier studies[8,34-38].

CONCLUSION

In present study we presented an association of NT-proBNP levels with CKD patients, which previously had only been confirmed by patients with LVD but not in patients without LVD. However it was concluded earlier and well supported by literature that increasing BNP levels is related to worsening heart failure, but has lacked clear recommendations regarding renal function[5,8]. After much deliberation and studies, it was than strongly suggested and recommended by several scientists and researchers that understanding the relationship of GFR, CKD and BNP in the presence and absence of clinical heart failure is beneficial to clinicians' understanding and interpretation of BNP and NT pro BNP levels when making diagnostic and treatment decisions. As suggested earlier that the goal of studies, such as ours, regarding assessment of NT pro BNP in CKD patients was to provide compelling evidence of the association of renal function and BNP[8]. However it was expected that additional prospective studies will be required to validate and better define this relationship. As concluded earlier[5,8,9], further studies are necessary and needed to confirm the outcome of assessments, such as presented here, in larger cohorts and to further validate cut-off values of NT pro-BNP in CKD patients with or without CHD/CHF. .

ACKNOWLEDGEMENTS

The authors wish to thank Prof Dr Carmen Wiley (USA), Prof Dr Rajat Tagore (Singapore) and Prof Dr Sascha David (Germany) for sharing valuable information and related articles for present study.

REFERENCES

1. Daniels LB, Maisel AS: Natriuretic peptides. *J Am Coll Cardiol.*, 2004; 50: 2357–2368.
2. Korenstein D, Wisnivesky JP, Wyer P, Adler R, Ponieman D, McGinn T: The utility of B-type natriuretic peptide in the diagnosis of heart failure in the emergency department: a systematic review. *BMC Emerg Med*., 2007; 7: 6.
3. Fuat A, Murphy JJ, Hungin AP, Curry J, Mehrzad AA, Hetherington A, Johnston JI, Smellie WS, Duffy V, Cawley P: The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *Br J Gen Pract*., 2006; 56: 327–333.
4. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL: Systolic and diastolic heart failure in the community. *JAMA*, 2006; 296: 2209–2216.
5. Tagore R, Ling LH, Yang H, Daw H-Y, Chan Y-H, Sethi SK. Natriuretic Peptides in Chronic Kidney Disease. *Clin J Am Soc Nephrol*., 2008; 3: 1644–1651.
6. McCullough PA, Duc P, Omland T, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Westheim A, Knudsen CW, Storrow AB, Abraham WT, Lamba S, Wu AH, Perez A, Clopton P, Krishnaswamy P, Kazanegra R, Maisel AS: B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing

Not Properly Multinational Study. *Am J Kidney Dis*., 2003; 41: 571–579.
7. Tsutamoto T, Wada A, Sakai H, Ishikawa C, Tanaka T, Hayashi M, Fujii M, Yamamoto T, Dohke T, Ohnishi M, Takashima H, Kinoshita M, Horie M: Relationship between renal function and plasma brain natriuretic peptide in patients with heart failure. *J Am Coll Cardiol*., 2006; 47: 582–586.
8. Wiley CL, Switzer SP, Berg RL, Glurich I, Dart RA. Association of B-Type Natriuretic Peptide (BNP) Levels With Estimated Glomerular Filtration Rate (eGFR) and Congestive Heart Failure (CHF). Rapid Release CM&R. doi:10.3121/cmr.
9. David S, Kumpers P, Seidler1 V, Biertz F, Hallern H, Fliser D. Diagnostic value of N-terminal pro-B-type natriuretic peptide(NT-proBNP) for left ventricular dysfunction in patients with chronic kidney disease stage 5 on haemodialysis. *Nephrol Dial Transplant*., 2008; 23: 1370–1377.
10. Zoccali C, Mallamaci F, Benedetto FA, Tripepi G, Parlongo S, Cataliotti A, Cutrupi S, Giacone G, Bellanuova I, Cottini E, Malatino LS: Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. *J Am Soc Nephrol*., 2001; 12: 1508–1515.
11. Takami Y, Horio T, Iwashima Y, Takiuchi S, Kamide K, Yoshihara F, Nakamura S, Nakahama H, Inenaga T, Kangawa K, Kawano Y: Diagnostic and prognostic value of plasma brain natriuretic peptide in non-dialysis-dependent CRF. *Am J Kidney Dis*., 2004; 44: 420–428.
12. Racek J, Kralova H, Trefil L Rajdl D, Eiselt J. Brain natriuretic peptide and Nterminal proBNP in chronic haemodialysis patients. *Nephron Clin Pract*., 2006; 103: c162–c172.
13. Khan IA, Fink J, Nass C, Chen H, Christenson R, deFilippi CR. N-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide for identifying coronary artery disease and left ventricular hypertrophy in ambulatory chronic kidney disease patients. *Am J Cardiol*., 2006; 97: 1530–1534.
14. Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, Lamb EJ.. B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis*., 2005; 46: 610–620.
15. Meguid El Nahas A, Bello AK: Chronic kidney disease: the global challenge. *Lancet,* 2005; 365: 331–340.
16. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ;. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*., 2005; 18: 1440–1463.
17. Khalifeh N, Haider D, Hörl WH. Natriuretic peptides in chronic kidney disease and during renal replacement therapy: an update. *J Investigative Med*., 2009; 57:33-39.
18. Felker GM, Petersen JW, Mark DB. Natriuretic peptides in the diagnosis and management of heart failure. *CMAJ,* 2006; 175: 611–617.
19. Goetze JP, Christoffersen C, Perko M Arendrup H, Rehfeld JF, Kastrup J, Nielsen LB. Increased cardiac BNPexpression associated with myocardial ischemia. *FASEB J*., 2007; 17: 1105–1107.
20. Konstam MA. Natriuretic peptides and cardiovascular events: more than a stretch. *JAMA*, 2007; 297: 212–214.
21. Wang AY, Lam CW, Yu CM, Wang M, Chan IH, Zhang Y, Lui SF, Sanderson JE.. N-terminal pro-brain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. *J Am Soc Nephrol*, 2007; 18: 321–330.
22. Suresh M, Farrington K. Natriuretic peptides and the dialysis patient. *Semin Dial*., 2005; 18: 409–419.
23. Fagugli RM, Palumbo B, Ricciardi D, Pasini P, Santirosi P, Vecchi L, Pasticci F, Palumbo R.. Association between brain natriuretic peptide and extracellular water in hemodialysis patients. *Nephron Clin Pract.,* 2003; 95: c60–c66.
24. Sharma R, Gaze DC, Pellerin D, Mehta RL, Gregson H, Streather CP, Collinson PO, Brecker SJ. Raised plasma N-terminal pro- B-type natriuretic peptide concentrations predict mortality and cardiac disease in end-stage renal disease. *Heart,* 2006; 92: 1518–1519.
25. Madsen LH, Ladefoged S, Corell P. N-terminal pro brain natriuretic peptide predicts mortality in patients with end-stage renal disease in hemodialysis. *Kidney Int.,* 2007; 1: 548–554.
26. Sheen V, Bhalla V, Tulua-Tata A, Schou M, Hildebrandt PR, Atar D. The use of B-type natriuretic peptide to assess volume status in patients with end-stage renal disease. *Am Heart J.,* 2007; 153: 244 e241–e245.
27. Barnes SC, Collinson PO, Galasko G, Lahiri A, Senior R. Evaluation of N-terminal pro-B type natriuretic peptide analysis on the Elecsys 1010 and 2010 analysers. *Ann Clin Biochem*., 2004; 41: 459–463.
28. Costello-Boerrigter LC, Boerrigter G, Redfield MM, Rodeheffer RJ, Urban LH, Mahoney DW, Jacobsen SJ, Heublein DM, Burnett JC Jr: Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. *J Am Coll Cardiol*., 47: 345–353.
29. Shi X, Xu G, Xia T, Song Y, Lin Q: N-terminal-pro-B-type natriuretic peptide (NT-proBNP): reference range for Chinese apparently healthy people and clinical performance in Chinese elderly patients with heart failure. *Clin Chim Acta*., 2005; 360: 122–127.
30. Masson S, Latini R, Anand IS, Vago T, Angelici L, Barlera S, Missov ED, Clerico A, Tognoni G, Cohn JN. Direct comparison of B-Type natriuretic peptide (BNP) and amino terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) Data. *Clin Chem*, 2006; 52:1528-1538.
31. Vickery S, Price CP, John RI, Abbas NA, Webb MC, Kempson ME, Lamb EJ. B-Type natriuretic peptide and amino terminal proBNP in patients with CKD: Relationship to renal function and left ventricular hypertrophy. *Am J Kidney Dis*, 2005; 46: 610-620.
32. deFilippi CR, Seliger SL, Maynard S, Christenson RH. Impact of renal disease on natriuretic peptide testing for diagnosing decompensated heart failure and predicting mortality. *Clin Chem*., 2007; 53: 1511-1519.
33. Mark PB, Stewart GA, Gansevoort RT, Petrie CJ, McDonagh TA, Dargie HJ, Rodger RS, Jardine AG. Diagnostic potential of circulating natriuretic peptides in chronic kidney disease. *Nephrol Dial Transplant*, 2006; 21:412-410.
34. Davis ME, Richards AM, Nicholls MG, Yandle TG, Frampton CM, Troughton RW. Introduction of metoprolol increases plasma B-type cardiac natriuretic peptides in mild,stable heart failure. *Circulation*, 2006; 113: 977-985.
35. van den Meiracker AH, Lameris TW, van de Ven LL, Boomsma F. Increased plasma concentration of natriuretic peptides by selective beta1-blocker bisoprolol. *J Cardiovasc Pharmacol*., 2003; 42: 462-468.

36. Lukowicz TV, Fischer M, Hense HW, Doring A, Stritzke J,Riegger G, Schunkert H, Luchner A; MONICA Investigators. BNP as a marker of diastolic dysfunction in the general population: Importance of left ventricular hypertrophy. *Eur J Heart Fail*., 2005; 7: 525-531.
37. Kanda H, Kita Y, Okamura T, Kadowaki T, Yoshida Y, Nakamura Y, Ueshima H. What factors are associated with high plasma B-type natriuretic peptide levels in a general Japanese population? *J Hum Hypertens*., 2005; 19: 165-172.
38. Tsuji H, Nishino N, Kimura Y, Yamada K, Nukui M, Yamamoto S, Iwasaka T, Takahashi H. Haemoglobin level influences plasma brain natriuretic peptide concentration. *Acta Cardiol*., 2004; 59: 527-531.