J Cardiovasc Thorac Res, 2019, 11(1), 14-18
doi: 10.15171/jcvtr.2019.03
http://jcvtr.tbzmed.ac.ir

Original Article

Utility of N-terminal pro-brain natriuretic peptide in detecting diastolic dysfunction in asymptomatic hypertensive patients: comparison with echocardiography

Sahadeb Prasad Dhungana[1*], Prahlad Karki[1], Madhab Lamsal[2]

[1]Division of Cardiology, Department of Internal Medicine, B.P. Koirala Institute of Health Sciences, Dharan, Nepal
[2]Department of Biochemistry, B.P. Koirala Institute of Health Sciences, Dharan, Nepal

Article info

Article History:
Received: 4 June 2018
Accepted: 11 February 2019
epublished: 13 March 2019

Keywords:
Echocardiography
Hypertension
Serum NT-proBNP

Abstract

Introduction: Data suggest that brain natriuretic peptide (BNP) and NT pro-BNP partially reflect ventricular pressure and could have a role in the early detection of diastolic abnormalities in hypertensive patients with normal systolic function. This study aimed to assess the role of NT pro-BNP for early detection of diastolic dysfunction in patients with hypertension and to correlate its level with echocardiographic parameters of diastolic dysfunction.

Methods: This is a comparative cross-sectional study. Hundred cases of asymptomatic hypertensive patients with normal left ventricular (LV) systolic function and 100 healthy subjects were subjected to echocardiography and measurement of serum NT-pro BNP who received care at outpatient department of internal medicine, B.P. Koirala Institute of health sciences, Nepal.

Results: Both systolic and diastolic blood pressures were significantly higher (≥160 and/or 100 mm Hg) in cases compared to controls (<120/80 mm Hg). Echocardiographic parameters of diastolic dysfunction: E/A ratio, E/E'ratio, deceleration time and isovolumetric relaxation time showed a significant difference between cases and controls. Mean serum NT-proBNP was significantly higher in patients with hypertension (213.19 ±184.3 pg/mL) compared to controls (58.51 ± 11.01 pg/mL) ($P=0.008$). There was no significant difference in mean serum NT-pro BNP levels between cases with no LV diastolic dysfunction (n=14) and controls (n=100) but it showed a significant difference between cases with LV diastolic dysfunction of all grades (n=86) and controls (n=100) ($P=0.00$). NT-proBNP levels were higher in both group of patients with E/A ratios <0.9 and 0.9-1.5 (245.72 ± 166.73 pg/mL and 210.69 + 143.53 pg/mL respectively) as compared to controls. Mean serum NT-proBNP levels were significantly higher in patients with IVRT >90 ms (270.43 ± 180.81 pg/mL) as compared to controls ($P=0.03$) but the difference was not significant between cases with IVRT of 60-90 ms (152.02 ± 100.23 pg/mL) and controls ($P=0.09$). NT-proBNP levels were significantly higher in all groups of patients with E/E' ratios <8, 8-12, >12 (197 ± 121.25 pg/mL, 263.12 ± 122.52 pg/mL and 180 ± 106.56 pg/mL respectively) compared to controls.

Conclusion: Mean serum NT-proBNP was significantly higher in patients with hypertension as compared to controls. There is some correlation between echocardiographic parameters of diastolic dysfunction and serum NT-proBNP. Hence, NT-proBNP may be useful for early detection of LV diastolic dysfunction in patients with hypertension.

Please cite this article as: Dhungana SP, Karki P, Lamsal M. Utility of N-terminal pro-brain natriuretic peptide in detecting diastolic dysfunction in asymptomatic hypertensive patients: comparison with echocardiography. **J Cardiovasc Thorac Res** 2019;11(1):14-18. doi: 10.15171/jcvtr.2019.03.

Introduction

Studies have provided evidence of a direct relationship between blood pressure and cardiovascular disease. Blood pressure is a major contributor of heart failure (HF) as 90% of new cases of HF in the Framingham Heart Study had earlier history of hypertension.[1] Diastolic HF is responsible for as many as 74% of cases of HF among patients with hypertension.[2] Despite this, this entity is rarely diagnosed because these patients have normal systolic function on echocardiogram. Detection of diastolic dysfunction in hypertensive patients is a major problem. Assessment of diastolic function is difficult and ideally requires cardiac catheterization, although non-invasive measure like echocardiogram is commonly

***Corresponding Author:** Sahadeb Prasad Dhungana, Email: drsadhu@gmail.com

used, they are non-specific. Although Doppler assessment of mitral inflow velocity pattern by echocardiogram[3] has been in use to assess left ventricular (LV) diastolic function, there are some limitations of this technique which suggest the need for other objective measures to look for diastolic abnormalities.[4] Addition of pulsed wave tissue Doppler imaging (TDI) has significantly enhanced the noninvasive assessment of diastolic function. This test is not easily available for routine diagnostic screening in resources limited areas. Therefore, alternative diagnostic procedures which will be helpful to detect diastolic dysfunction is necessary.

Natriuretic peptides are natriuretic hormones released primarily from ventricles of the heart. The serum concentration of natriuretic peptides gets raised in both asymptomatic and symptomatic patients with LV dysfunction, allowing their use in diagnosis.[5] Data suggest that serum brain natriuretic peptide (BNP) and N terminal pro-BNP (NT pro-BNP) partly reflects ventricular pressure, so we hypothesized that BNP and NT pro-BNP levels could have a role in the early detection of diastolic abnormalities in hypertensive patients. Therefore, we performed this study to assess the role of NT pro-BNP for early detection of diastolic abnormalities in asymptomatic hypertensive patients and to correlate its serum concentration level with echocardiographic measures of diastolic dysfunction.

Materials and Methods

This is a comparative cross-sectional study which included 100 asymptomatic hypertensive patients. Inclusion criteria was systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg on 2 or more measurements taken at least 60 minutes apart. Enrolled patients had normal LV systolic function, defined as LV ejection fraction >55%, with no major wall motion abnormalities, except for LV hypertrophy on echocardiogram, no clinical symptoms or signs of heart failure or other acute or chronic target organ damage related to hypertension. Also one- hundred age and sex-matched apparently healthy subjects (controls) whom we selected among the accompanying attendants of patients in cardiology clinic of B.P. Koirala Institute of Health Sciences (BPKIHS), Dharan, Nepal from July 2015 to June 2016 were selected. We included controls in this study to look for the prevalence of diastolic dysfunction among apparently healthy people detected by echocardiogram and to get the reference value of serum NT pro-BNP in our healthy population so that we make a comparison with hypertensive patients who are known to have a higher prevalence of diastolic dysfunction. There was no cut off value of serum NT-pro BNP for diagnosis of diastolic dysfunction.

Echocardiography

All hypertensive patients and controls underwent M-Mode, 2 dimensional (2D), color flow and pulsed wave Doppler transthoracic echocardiogram by Philips IE33 echo machine. Qualified registered cardiologist performed the echocardiogram and again reconfirmed by another cardiologist. We measured pulsed wave Doppler recordings in the apical four chamber view from a 4 x 4 mm sample volume placed at the tips of mitral leaflets. The transmitral pulsed Doppler velocity readings from three consecutive cardiac cycles used to derive peak velocities in the early part of diastole (E) and contraction of the atrium (A). We measured deceleration time (DT) as the interval from the E wave to identify declining velocity regarding to baseline. We obtained LV isovolumic relaxation time (IVRT) in milliseconds from the apical 5-chamber view with a pulsed Doppler sample volume positioned to straddle the LV outflow tract and mitral orifice to get signals from aortic valve closure. If diastolic abnormalities were present with any of these three measures i.e. conventional Doppler recordings, the effects of the Valsalva maneuver on transmitral flow velocities or TDI based on criteria for the diagnosis of diastolic dysfunction,[6] the subjects were considered to have LV diastolic dysfunction.

Measurement of serum NT- proBNP

After a resting period for 20 minutes, we drew 10 ml blood in a plain tube from an antecubital vein from the subjects under study for serum NT- proBNP measurement. After centrifugation at 2500 rpm for 5 minutes, we took serum for NT- proBNP measurement immediately or was kept at -40°C if delayed. We used the VIDAS instrument using Enzyme-linked Fluorescent assay (ELFA) technique for serum NT-proBNP measurement. VIDAS NT-proBNP is an automated quantitative test for the determination of human serum or plasma NT-proBNP.

We entered collected data in Microsoft Excel 2007 and converted into SPSS 20 version. We applied Independent t-test to find out the significant differences between groups (cases and controls) and within the group at a 95% confidence interval. Pearson correlation statistics measured the degree of relationship between serum NT-proBNP values and echocardiographic parameters.

Results

Table 1 shows the baseline characteristics of all 200 patients (100 cases and 100 controls). Systolic, diastolic and mean arterial blood pressures were significantly higher (hypertensive range) in cases compared to controls. Echocardiographic parameters of diastolic dysfunction like E/A ratio, E septal and lateral velocity, E/E', DT, IVRT showed the significant difference between cases and controls as shown in Table 2. The level of mean serum NT-proBNP was significantly higher in patients with hypertension compared to healthy controls. There was no significant difference in mean serum NT-proBNP levels between cases with no left ventricular diastolic dysfunction (n=14) and controls (n=100) but it shows the statistically

Table 1. Baseline characteristics and echocardiographic measures of patients with asymptomatic hypertensive patients vs healthy controls

Characteristics	Cases (n=100)	Control (n=100)	*P* value
Age (y)	52.0 ± 9.5	48.3 ± 7.1	0.90
Sex (male: female)	54:46	59:41	0.15
BMI (kg/m^2)	23.7 ± 1.8	22.0 ± 1.7	0.72
Heart rate (BPM)	75.4 ± 6.2	74.5 ± 5.7	0.82
SBP (mm Hg)	152.4 ± 11.7	114.9 ± 8.1	0.00
DBP (mm Hg)	93.6 ± 8.4	76.7 ± 7	0.00
Mean BP (mm Hg)	113.3 ± 7.6	92.8 ± 6.2	0.00
Hemoglobin (gm/dL)	11.8 ± 1.02	12.9 ± 0.9	0.82
Sodium (meq/L)	138.9 ± 4.5	140 ± 2.1	0.90
Potassium (meq/L)	4.4 ± 0.4	4.5 ± 0.7	0.82
Serum urea (mg/dL)	15 ±12	14 ± 10	0.82
Serum creatinine (mg/dL)	0.8 ± 0.32	0.9 ± 0.2	0.71
LVH by echocardiography	75	0	0.00
LVH by electrocardiography	40	0	0.00

BMI: body mass index; BPM: beat per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVH: left ventricular hypertrophy.

Table 2. Echocardiographic measures of left ventricular diastolic function and serum concentration of NT-proBNP of cases vs healthy controls

	Cases (n=100)	Controls (n=100)	*P* value
Normal LV diastolic function (n)	14	84	0.00
LV diastolic dysfunction (n)	86	16	0.00
E/A	0.8 ± 0.2	1.1 ± 0.2	0.00
E lateral	7.3 ± 1.5	13.2 ± 1.9	0.00
E septal	8.1 ± 1.1	12.3 ± 1.5	0.00
E/E'	9.1 ± 2.0	6.8 ± 0.8	0.00
DT (ms)	198.4 ± 27.1	203.1 ± 1	0.00
IVRT (ms)	94.7 ± 18.9	84.6 ± 6.4	0.00
NT-proBNP (pg/mL)	213 ± 184.3	58.5 ± 11.0	0.00

LV: left ventricle; E: peak velocity in early diastole; A: peak velocity after atrial contraction; E': early mitral annular tissue diastolic velocity, DT: deceleration time; IVRT: Isovolumetric relaxation time; NT-proBNP: N terminal pro brain type natriuretic peptide.

significant difference between cases with left ventricular diastolic dysfunction of all grades (n=86) and controls (n=100). Table 3 represents the mean serum NT-proBNP levels in the normal and abnormal diastolic function groups. The difference between groups was significant as patients diagnosed with abnormal diastolic function (n=102) had a mean serum NT-proBNP concentration of 187.6 ± 117.9 pg/mL whereas the patients with normal diastolic function (n=98) had a mean concentration of 60.1 ± 22.08 pg/mL. NT pro-BNP levels were significantly higher in all groups of patients with E/E' ratios <8, 8-12, >12 (197 ± 121.25 pg/mL, 263.12 ± 122.52 pg/mL and 180 ± 106.56 pg/mL respectively) as compared to healthy controls (58.51 ± 11.01 pg/mL) (*P* value <0.015) as shown in Figure 1. However, the difference was not significant among patient groups with E/E'<8, 8-12 and >12. The non-significant higher values in cases with E/E' <8

Table 3. Comparison of Serum NT-proBNP between cases and controls

	Serum NT-proBNP (pg/mL)		
	Cases (n=100)	Control (n=100)	*P* value
No LVDD (n=14)	68.3±51.6	58.5±11	0.99
Grade I LVDD (n=77)	197.3 ± 95.7	58.5±11	0.00
Grade II LVDD (n=9)	351±118.2	58.5±11	0.00

LVDD: left ventricular diastolic dysfunction.

compared to cases with >12 could be due to by chance or small sample size.

Mean serum NT-proBNP levels were significantly higher in patients with IVRT >90 ms (270.43 ± 121.3 pg/mL) as compared to healthy controls (58.51 ± 11.01 pg/mL) (*P*=0.03) but the difference was not significant between cases with IVRT of 60-90 ms (152.02 ± 102.2 pg/mL) and controls (58.51 ± 11.01 pg/mL) (*P* =0.09). NT-proBNP levels were higher in both group of patients with E/A ratios <0.9 and 0.9-1.5 (245.72 ± 166.7 pg/mL and 210.69 ± 143.53 pg/mL respectively) as compared to healthy controls (58.51 ± 11.01 pg/mL).

Figure 2 represents the mean serum NT-proBNP levels in the normal and abnormal diastolic function groups. The difference between groups was significant. Patients diagnosed with abnormal diastolic function (n=102) had mean serum NT-proBNP concentration of 187.6 ± 113.9 pg/mL whereas the patients with normal diastolic function (n=98) had a mean concentration of 60.1 ± 22.08 pg/mL. Table 4 shows the correlation of serum NT-proBNP level with blood pressure and echocardiographic parameters of hypertensive patients.

Discussion

The results of this study show that raised serum concentration of NT-proBNP represents a serum marker providing positive evidence of the presence of a diastolic impairment in patients with asymptomatic

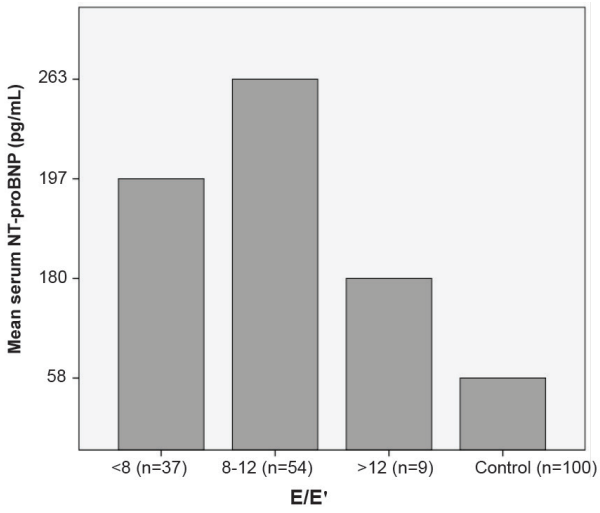

Figure 1. Serum NT-proBNP expressed as reflection of E/E' ratios. Values are expressed as mean. NT-proBNP is higher in cases (E/E'<8, 8-12 and >12 groups) as compared to controls (*P* value <0.015)

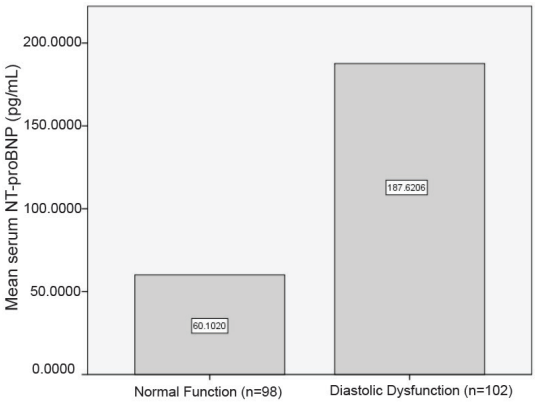

Figure 2. Serum NT-proBNP levels in patients with normal diastolic function (n=98) and diastolic dysfunction (n=102)

systemic hypertension. Echocardiographic indicators of diastolic dysfunction like E/A ratio, DT, E/E' and IVRT demonstrated a significant difference between cases and controls. These various echocardiographic parameters of diastolic dysfunction correlated with the serum concentration of NT-proBNP. The level of mean serum NT-proBNP was significantly higher in patients with hypertension as compared to healthy controls.

Diastolic dysfunction in hypertension is common and usually accompanied by left ventricular hypertrophy (LVH). Our study showed that 75% of cases of hypertension had echocardiographic evidence of LVH and 40% met electrocardiographic criteria of LVH which is more or less similar to the results of a previous study.[7] Eighty-six percent of our hypertensive patients had diastolic abnormalities in contrast to 16% of healthy controls. This higher prevalence of LVH and LV diastolic dysfunction in our asymptomatic hypertensive population could be due to long-standing undiagnosed hypertension, lack of awareness and screening program in our community.

Doppler trans-mitral velocity measurements have become the foundation for the diagnosis of diastolic dysfunction.[8] However, pitfalls in the echo-Doppler assessment of diastolic dysfunction exist. A simple, rapid blood test that reflects diastolic dysfunction would be of significant clinical benefit.

A study has demonstrated that BNP can predict the absence or presence of LV dysfunction as seen in echocardiogram and might be used as a screening tool for the detection of LV dysfunction and which may, in fact, obviate the need for echocardiogram.[9] Our study reveals significantly higher serum level of mean serum NT-proBNP in patients with LV diastolic dysfunction of all grades (n=86) compared to controls (n=100) indicating that NT-proBNP could be a valuable test to easily rule out the diastolic dysfunction in asymptomatic hypertensive patients with early mild diastolic dysfunction.

Studies suggest that age and gender may influence circulating natriuretic peptide levels.[10,11] Our study didn't show the significant difference in serum NT-proBNP concentration between genders and among different age groups in both cases and healthy controls. This could be due to the small sample size. Likewise, our study did not show the significant difference in serum NT-proBNP concentration among patients with different body mass index since the obese population has lower circulating NT-proBNP and BNP levels.[12]

Table 4. Correlation of serum NT-proBNP (213.1 ± 184.3 pg/mL) level with blood pressure and echocardiographic parameters of hypertensive patients (N=100)

Parameters	Mean	r	*P* value
Age (y)	52.0 ± 9.5	-0.09	0.37
BMI (kg/m^2)	23.7 ± 1.8	-0.03	0.72
Heart rate (BPM)	75.4 ± 6.2	-0.00	0.97
Systolic blood pressure (mm Hg)	152.8 ± 11.3	0.12	0.23
Diastolic blood pressure (mm Hg)	93.6 ± 8.4	0.19	0.05
Mean blood pressure (mm Hg)	113.3 ± 7.6	0.22	**0.02**
E/A	1.02 ± 0.2	-0.13	0.17
E/E'	9.1 ± 2.0	-0.01	0.92
DT (ms)	198.4 ± 27.1	0.21	**0.03**
IVRT (ms)	94.7 ± 18.9	0.26	**0.00**
LVEF (%)	66.0 ± 5.4	0.07	0.46

BMI: body mass index; BPM: beat per minute; mmHg: millimeter of mercury; E: peak velocity in early diastole; A: peak velocity after atrial contraction; E': early mitral annular tissue diastolic velocity, DT: Deceleration time; IVRT: Isovolumetric relaxation time; NT-proBNP: N terminal pro-brain-type natriuretic peptide, LVEF: left ventricular ejection fraction

A study has shown an association between plasma BNP levels and blood pressure variability and found that BNP level correlated with mean blood pressure.[13] Similarly, in our study, serum NT-proBNP levels positively correlated with mean arterial blood pressure among hypertensive patients (r =0.22), (*P* value = 0.02). This could be explained by the release of an increased amount of BNP by pressure-overloaded LV due to higher mean blood pressure.

With increasing age, the mitral E velocity and E/A ratio decrease, whereas DT and A velocity increase. This can lead to over-diagnosis of diastolic dysfunction without increased LV filling pressure in elderly patients. NT-proBNP could be of value to mitigate this problem. In our study, NT-proBNP levels were higher in both group of patients with E/A ratios <0.9 and 0.9-1.5 as compared to healthy controls. This indicates that serum NT-proBNP level correctly diagnoses the impaired diastolic dysfunction with increased LV filling pressure.

E/E' ratio has long been considered as the best parameter for the diagnosis of diastolic HF and it could be used for estimation of LV filling pressures.[14] Lubian et al[15] found increased serum concentration of NT-proBNP levels in patients with diastolic dysfunction but differences between hypertensive and non- hypertensive patients without diastolic dysfunction was not significant. This indicates that, in our patients with hypertension, the level of NT-proBNP increased because of changes in diastolic function. In other words, NT-proBNP levels in

hypertensive patients probably increase due to diastolic dysfunction.

In this study, serum concentration of NT-proBNP levels was significantly higher in all groups of patients with E/E' ratios <8, 8-12 and >12 as compared to healthy controls. The increased concentration in cases with E/E' <8 in this study could be due to that hypertensive patients with normal filling pressure may have higher serum concentration of NT-proBNP levels or due to by chance owing to small sample size which needs further study.

In patients with diastolic dysfunction, LV pressure falls slowly which leads to delayed opening of the mitral valve and prolongation of IVRT.[6] In this study, mean serum concentration of NT-proBNP levels were significantly higher in patients with IVRT >90 ms as compared to healthy controls ($P=0.03$) which indicate that these hypertensive patients have an echocardiographic measure of impaired myocardial relaxation who had increased serum concentration of NT-proBNP.

Limitations

This is a comparative cross-sectional study in a limited number of asymptomatic patients of hypertension. Moreover, we enrolled cases and controls in a consecutive manner rather than randomization. We measured serum NT-proBNP at a point of time when patients presented with severe hypertension and did not look at the effect when blood pressure is well controlled.

Conclusion

Serum concentration of NT-proBNP in the setting of normal LV systolic function correlates with the absence or presence of diastolic abnormalities detected by echocardiogram. A low NT-proBNP level may obviate the need for an echocardiogram in some patients. An elevated serum NT-proBNP level is an indication of the presence of LV dysfunction warranting further cardiac workup. This study demonstrated that NT- proBNP could be of help for the detection of LV diastolic dysfunction in asymptomatic patients with hypertension. Future large studies would be needed to decide whether serum NT-proBNP levels might be part of one of the diagnostic modalities for the diagnosis of diastolic dysfunction in patients with hypertension.

Ethical approval

This study was approved by the Institutional Review Committee (IRC).

Competing interests

All authors declare no competing financial interests exist.

References

1. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. **JAMA** 1996; 275(20):1557-62.
2. Vasan RS, Benjamin EJ, Levy D. Prevalence, clinical features and prognosis of diastolic heart failure: an epidemiologic perspective. **J Am Coll Cardiol** 1995; 26(7):1565-74.
3. Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography: part I. Physiologic and pathophysiologic features. **Mayo Clin Proc** 1989; 64(1):71-81.
4. Grodecki PV, Klein AL. Pitfalls in the echo-doppler assessment of diastolic dysfunction. **Echocardiography** 1993; 10(2):213–34.
5. Kinnunen P, Vuolteenaho O, Ruskoaho H. Mechanisms of atrial and brain natriuretic peptide release from rat ventricular myocardium: effect of stretching. **Endocrinology** 1993; 132(5):1961-70.
6. Armstrong WF, Ryan T. Feigenbaum's Echocardiography. 7th ed. Lippincott Williams & Wilkins: Wolters Kluwer Publisher; 2011.
7. Prakash O, Karki P, Sharma SK. Left ventricular hypertrophy in hypertension: Correlation between electrocardiography and echocardiography. **KUMJ** 2009; 7(26):97-103.
8. Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular function: new insights from a combined hemodynamic and Doppler echocardiographic study. **J Am Coll Cardiol** 1988; 12:426–40.
9. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. **N Engl J Med** 2002; 347:161-7.
10. Luchner A, Burnett JC, Jougasaki M, et al. Evaluation of BNP as a marker of left ventricular dysfunction and hypertrophy in the population. **J Hypertens** 2000; 18:1121-8.
11. Sayama H, Nakamura Y, Saito N, Kinoshita M. Why is the concentration of plasma BNP in elderly inpatients greater than normal? **Coron Artery Dis** 1999;10:537-40
12. Krauser DG, Lloyd-Jones DM, Chae CU, et al. Effect of BMI on natriuretic levels in patients with acute heart failure: PRIDE sub-study. **Am Heart J** 2005; 149(4):744-50.
13. Masugata H, Senda S, Inuki M, et al. Analysis of association between BNP levels and blood pressure variability. **Exp Ther Med** 2014; 8(1):21-24.
14. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the ehocardiographic evaluation of left ventricular diastolic function by echocardiography. **J Am Soc Echocardiogr** 2009; 22(2):107-33.
15. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, et al. Utility of B- natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. **Circulation** 2002;105:595-601.