The Differences of Average Level Serum N Terminal Prob-Type Natriuretic Peptide (NT-PROBNP) in Hypertension Patients with and without Left Ventricular Hypertrophy At Cardiology Outpatients Dr. Sardjito General Hospital Yogyakarta

Gusti Hariadi Maulana[1], Lucia Krisdinarti[2], Hariadi Hariawan[2]

[1]Speciality Training Program of Internal Medicine, Faculty of Medicine,
Universitas Gadjah Mada-Dr. Sardjito General Hospital
[2]The Division of Cardiology, Department of Internal Medicine, Faculty of Medicine,
Universitas Gadjah Mada-Dr. Sardjito General Hospital

ABSTRAK

Abstrak. Hipertensi menyebabkan perubahan dalam struktur dan fungsi cardial sebagai pemicu perubahan neurohormonal dan pembuluh darah pada hipertrofi jantung konsentris. Ekspansi volume miosit atau peningkatan tekanan akan memicu sintesis pra-proBrain Natriuretic Peptide (BNP) dalam miokardium ventrikel. Pre-proBNP akan dikonversi menjadi proBNP sedangkan proBNP akan dikonversi ke dalam bentuk BNP dan N-terminal proBNP (NTproBNP).
Tujuan. Penelitian ini bertujuan untuk mengetahui perbedaan BT pro BNP pada pasien hipertensi tanpa LVH dan pasien hipertensi dengan hipertrofi ventrikel kiri.
Metode. Desain penelitian adalah potong lintang di poliklinik kardiologi rawat jalan di Rumah Sakit Dr. Sardjito Yogyakarta dari bulan Agustus 2009 sampai jumlah sampel terpenuhi. Untuk menganalisis perbedaan antara dua kelompok pasien hipertensi menggunakan uji t-test untuk distribusi normal, sedangkan untuk distribusi normal dianalisis dengan uji Mann-Whitney U. Untuk menganalisis normalitas data dilakukan uji Kolmogorov-Smirnov. Perbedaan dua kelompok pasien hipertensi dianggap signifikan jika $p < 0,005$ dengan interval kepercayaan 95%.
Hasil. Hasil penelitian menunjukkan 73 subyek penelitian dikelompokkan menjadi 2 kelompok yaitu kelompok hipertensi tanpa LVH (31 subyek) dan dengan LVH (42 subyek) berdasarkan parameter ekokardiografi (IVSD, LVPWd, LVIDd, LVM, dan LVMI) yang terdiri dari 24 laki-laki dan 49 perempuan. Karakteristik dasar antara kelompok hipertensi dengan dan tanpa LVH tidak berbeda secara signifikan baik dalam usia, BMI, tekanan darah, durasi karakteristik terapi hipertensi dari penggunaan obat-obatan seperti ACEI, ARB, β-blocker, CCB, spironolactone dan furosemide. Rerata tingkat NT proBNP pada kelompok hipertensi tanpa LVH (46,60±45,51) dan hipertensi dengan kelompok hipertrofi ventrikel kiri (201,60 ±192,30 ng/ml). Dari hasil uji Kolmogrov-Smirnov hasil bahwa distribusi data tidak normal sehingga digunakan uji Mann-Whitney U, memperoleh perbedaan yang signifikan secara statistik.
Kesimpulan. Ada perbedaan yang signifikan dalam tingkat rata-rata serum NT proBNP pada pasien hipertensi tanpa LVH dan pasien hipertensi dengan hipertrofi ventrikel kiri.

Kata kunci*: hipertensi, hipertrofi ventrikel kiri (LVH), N-terminal proBrain natriuretik Peptida*

ABSTRACT

Introduction. Hypertension cause changes in the structure and function of cardial as triggers neurohormonal and vascular changes that concentric cardiac hypertrophy. Myocyte volume expansion or increased pressure will trigger the synthesis of pre-proBrain Natriuretic Peptide (BNP) in the ventricular myocardium. Pre-proBNP will be converted into proBNP and proBNP will be converted into the form of BNP and N-terminal proBNP (NT proBNP).
Aim. This study aimed to determine differences in BT pro BNP in hypertensive patients without LVH and hypertensive patients with LVH. The study design was cross-sectional in cardiology polyclinic`s outpatient at Dr. Sardjito General Hospital Yogyakarta from August 2009 until the sample number is fulfilled.
Method. To analyze the difference between the two groups of hypertensive patients using the t-test for normal distribution, while for abnormal distribution were analyzed with the Mann-Whitney U test. To analyze the normality of data conducted by Kolmogorov-Smirnov. The differences of two groups of hypertensive patients considered as significant if $p < 0.005$ with confidence interval of 95%.
Results. The results showed 73 study subjects grouped subjects into 2 groups: hypertensive subjects without LVH (31 subjects) and with LVH (42 subjects) based on echocardiography parameters (IVSD, LVPWd, LVIDd, LVM, and LVMI) consisting of 24 males and 49 females. The baseline characteristics between the study groups of hypertensive subjects with and without LVH did not differ significantly either in age, BMI, blood pressure, duration of hypertention therapeutic characteristics of the use of drugs such as ACEI, ARB, β-blocker, CCB, spironolactone and furosemide. Mean NT proBNP levels in hypertensive group without LVH (46.60 ± 45.51) and hypertention with LVH group (201.60 ±192.30 ng/ml). From the results of the Kolmogrov-Smirnov test result that the data distribution was not normal then used Mann-Whitney U test, obtained a statistically significant differences.
Conclusion. There were significant differences in the mean levels of serum NT proBNP in hypertensive patients without LVH and hypertensive patients with LVH.

Keywords: *hypertension, left ventricular hypertrophy (LVH), N-terminal proBrain natriuretic Peptide*

INTRODUCTION

World Health Organization (WHO) reported that the systolic blood pressure > 115 mmHg is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease with slight variations influenced by gender. In the end that is not optimal blood pressure is a risk factor for all-cause mortality in the world.[1]

The prevalence of hypertension in Indonesia in 2007 was 32.2%, and the highest prevalence was found in the province of South Kalimantan (39.6%), the lowest in West Papua (20.1%). Socio-demographic factors were found at risk for hypertension were age, gender, education and employment, behavioral risk factors are at risk for hypertension is first ever smoking, alcohol consumption one last month, one time consumption of caffeinated beverages per day, and less physical activity, risk factors physical risk for hypertension is obesity and obesity abdominal.[2]

Essential hypertension is a major risk factor for cardiovascular disease. Terminal kidney disease incidence and prevalence of heart failure also increases with the presence of hypertension and blood pressure control is not adequate.[3,4,5]

One of complications of hypertension is the occurrence of ventricular hypertrophy in the left (Left Ventricular Hypertrophy). Left ventricular hypertrophy is marked by hypertrophy concentric with hypertrophy circumferential miofibril, contractility which increased, an increase in thickness of wall

ventricular, volume at the end of diastolic are low, and disturbances relaxation (diastolic dysfunction). On 30-50% individuals with hypertension degrees I and II have left ventricular relaxation disorders, and on hypertension with degrees who more heavier, 2/3 of patients had abnormal relaxation left ventricular.[1,6] Expansion volume or pressure myocytes which increased, resulted in the stretch on ventricular wall so that triggering synthesis of pre-proBrain Natriuretic Peptide (BNP) in myocardium ventricle. Pre-proBNP will later be converted into proBNP and proBNP will converted into form of BNP and N-terminal proBNP (NT proBNP). The release of BNP and NT proBNP will fix the relaxation myocardium and have an important role in the responding an acute increase volume ventricular with counteract the effects vasoconstriction, retention, and effects antidiuresis from system renin-angiotensin which activated.[7,8,9,10]

LITERATURE REVIEW

Myocyte hypertrophy is a compensatory response of increased afterload. Mechanical and neurohormonal stimulation that accompany hypertension may activate myocardial cell growth, gene expression and subsequently left ventricular hypertrophy. Activation of the renin angiotensin system causes the growth of cells and interstitial matrix components, so that LVH is caused by myocyte hypertrophy and myocyte imbalance between myocardial interstitial skeletal structure. Two major factors that trigger hypertrophy is a biomechanical stress and neurohumoral factors. According to the law of Laplace, afterload induced increase in systolic wall stress which offset an increase in thickness of the ventricular wall of the heart. Ion channels that are sensitive to the plasma membrane indicated strain kardial myocytes. The myocyte stretch induces the synthesis and secretion of several growth factors including insulin-like growth factor-I, angiotensin II and endothelin I, and humoral factors is sufficient to induce myocyte hypertrophy. Humoral factors such as angiotensin II, aldosterone, noradrenaline and endothelin directly induce hypertrophy and status associated with maladaptive processes to increase myocardial fibrosis in ventricular hypertrophy.[4]

Remodeling is a change in the structure (dimensions, mass, shape) and function of the heart (called remodeling cardiac or ventricular) as a result of hemodynamic load and cardiac or injury associated with neurohormonal activation. Remodeling is often divided into physiological or pathological or classified adaptive and maladaptive.[4]

Remodeling associated with cellular changes including myocyte hypertrophy, myocyte loss due to apoptosis or necrosis and fibroblast proliferation and fibrosis. Although the pathways and cellular involvement in LV remodeling are not fully understood, the molecular mechanisms at the level of the strain is myocytes, there is increased production or release of angiotensin II, norepinephrine and endothelin, stimulates neurohormonal changes in protein expression and myocyte hypertrophy, increased angiotensin II, aldosterone and stimulates cytokine synthesis of collagen, causing fibrosis and extracellular matrix remodeling. Reduction of nitric oxide bioactivity effect on cell growth and interstitial, at normal levels inhibit remodeling. The end result of this research is a pathological remodeling of cardiac damage and increased neurohormonal activation.

Remodeling and myocardial changes play a role in the pathogenesis of ventricular arrhythmias.[10]

There are 3 major groups natriuretic peptide, namely atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Natriuretic peptide is the characteristic biochemical structure that consists of 17 amino acid ring and a disulfide bond between two cysteine molecules. B-type natriuretic peptide is also called brain-type natriuretic peptide, is first discovered in 1988 after isolated from pig brain. Soon after the discovery, the BNP is a cardiac hormone that comes from the heart.[7,8]

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) is known as an antagonist of the renin-angiotensin system. C-type natriuretic peptide (CNP) is a new member of natriuretic peptide group but the difference of the main source in the vascular endothelium. Unlike ANP and BNP, CNP does not have direct natriuretic activity. This is because CNP is a selective agonist for the B-type natriuretic receptor whereas ANP and BNP are selective for the A-type natriuretic receptor.[8]

Major stimulus for the release of BNP is increased myocardial stress due to increase volume or pressure, increased efforts mechanical (mechanical effort), neurohormonal factors such as endothelin, angiotensin II, adrenal steroids, inflammatory cytokines, growth factors, prostaglandins, thyroid hormone, and alpha-adrenergic agents. Although the release of BNP occurs under normal circumstances, increased regulation could occur in a state of volume overload.[15]

METHODS

This study was a cross-sectional study were performed at the Cardiology outpatient Dr. Sardjito General Hospital Yogyakarta and Clinical Pathology Laboratory Dr. Sardjito Yogyakarta. The study began in August 2009.

The study population was patients attending Cardiology outpatient Dr. Sardjito General Hospital Yogyakarta. As the sample was hypertensive patients at the Cardiology outpatient dr. Sardjito General Hospital Yogyakarta diagnosed by JNC VII criteria. Study subjects were recruited by consecutive sampling method.

Inclusion criteria for the study were all hypertensive patients who have been diagnosed based on the criterias of JNC VII 2003, in the treatment of hypertensive patients, stated were willing to participate in this study and signed a letter of informed consent or informed consent of research subjects as well as both medical measures blood sampling.

Exclusion criteria included acute coronary syndrome, primary valvular heart disease, permanent arrhythmia, obesity, diabetes mellitus, chronic renal disease, hyperthyroidism, anemia, and stroke.

Estimates of the 24 samples in each group were considered adequate to detect differences in levels of NT-proBNP in hypertension with left ventricular hypertrophy and without left ventricular hypertrophy. Data presented in the form of mean and standard deviations (mean ± standard deviation). The difference between the mean values of continuous data were analyzed with the unpaired Student t-test for normal distribution, while the distribution was not normal was analyzed by the Mann-

		Examiner 1		
		With LVH	Without LVH	Total
Examiner 2	With LVH	A 7	B 2	9
	Without LVH	C 1	D 10	11
	Total	8	12	20

Picture 1. *Kappa*

Table 1. Basic Characteristics of subject

Variabel	With left ventricle hypertrophy n = 42	Without left ventricle hypertrophy n = 31	P
Age (years)	50.70 ± 11.40	59.80 ± 12.20	0.7
Sex			0.8
Male n (%)	13 (31.00)	11 (35.50)	
Female n (%)	29 (69.00)	20 (64.50)	
IMT kg/m^2	25.00 ± 3.16	24.30 ± 3.40	0.3
TDS mmHg	145.00 ± 18.20	145.00 ± 14.20	0.9
TDD mmHg	88.00 ± 10.40	88.00 ± 8.40	0.9
HR x/mnt	76.70 ± 10.80	76.10 ± 5.50	0.7
Hypertension			0.7
Stage I n (%)	40 (55.60%)	33 (44.40%)	
Stage II n (%)	47 (65.00%)	26 (35.00%)	
Long suffered (years)	9.50 ± 6.90	8.50 ± 6.70	0.5

Table 2. Therapy characteristics of subject

Variable	With left ventricle Hypertrophy n = 42	Without left ventricle hypertrophy n = 31	P
ACEI n (%)	24 (57.10)	12 (38.70)	0.1
ARB n (%)	11 (26.20)	13 (41.90)	0.2
B-Blocker n (%)	9 (21.40)	5 (17.20)	0.7
CCB n (%)	9 (21.40)	7 (24.10)	0.7
Furosemid n (%)	26 (61.90)	10 (31.00)	0.1
Spironolactone n (%)	4 (9.5)	1 (3.4)	0.6
Drug use			
Without drug (%)	8.00	10.00	
1 drug (%)	64.00	60.00	0.98
2 drug (%)	20.00	20.00	
3 drug (%)	8.00	1000	

Table 3. Parameters used in measuring left ventricular hypertrophy

Variable	With left ventricle hypertrophy n = 42	Without left ventricle hypertrophy n = 31	P
EF % (Mean±SD)	65.50 ± 8.00	67.7 ± 6.30	0.2
IVSD mm (Mean±SD)	1.30 ± 0.20	1.0 ± 0.10	0.00
LVPWd mm(Mean±SD)	1.20 ± 0.10	1.0 ± 0.10	0.00
LVIDd mm (Mean±SD)	4.7 ± 0.50	4.3 ± 0.30	0.02
LVM g/m^2 (Mean±SD)	250.50 ± 74.10	160.20 ± 27.00	0.00
LVMI g/m^2(Mean±SD)	155.10 ± 40.70	100.0 ± 13.0	0.00

Table 4. Differences of level NT proBNP

Variable	With left ventricle hypertrophy	Without left ventricle hypertrophy	P
NT proBNP (pg/ml)	201.60 ± 192.30	46.6 ± 45.10	0.00 *

Exp : * *Mann Whitney U test,* significant if p < 0.05.

Whitney U test. Categorical data discrepancies with Chi Square test. Data were presented with 95% confidence interval and P value> 0.05 was statistically significant.

RESULT AND DISCUSSION

Obtained 73 subjects with hypertension without left ventricular hypertrophy (31 subjects) and hypertension with left ventricular hypertrophy (42 subjects). Study subjects consisted of 24 (32.87%) men and 49 (67.13%) were women.

Figure 1 is a table showing the suitability 2x2 echocardiography examination by 2 examiners. From the above calculation kappa value of 0.69 is obtained, which means the power of inter-observer agreement (inter-examiner) is quite high (satisfactory or good category).

Table 3 shows the parameters used in measuring left ventricular hypertrophy in subjects research.

Age factor does not affect the outcome of the study between the two groups. Role in the life of considerable geometric changes and left ventricular mass, especially in patients with essential hypertension often occurs in the elderly, male gender, hypertension is severe degrees of hypertension, has been suffering from hypertension more than a year, in obese patients and patients with DM.[11]

Gender factor has no effect in this study because it was not found significant differences (p=0.8). Women will be better protected from cardiovascular disease and hypertension due to differences in estrogen and androgen hormone balance and also associated with the RAS system primarily AT2 receptor is expressed lower in male rats that facilitate the occurrence of cardiovascular disease and hypertension.[12] But in this study the age range most fall into menopause age.

Relationship of obesity and hypertension complex, multifactorial mechanisms including activation of the sympathetic system and renin, insulin resistance, abnormal renal

sodium regulation, and the possibility of leptin resistance and natriuretic peptides.

Data from systolic and diastolic blood pressure in both groups subjects not found a significant difference (p=0.9) so that it can be concluded that the effect of high blood pressure on the outcome of research that NT proBNP was similar in both groups of subjects.

Long suffered from hypertension between the two groups were similar in this study. In another study concluded that long hypertension associated with left ventricular hypertrophy (p <0.001) so that the length of suffering from hypertension is a strong predictor of the occurrence of left ventricular hypertrophy.[13]

Use of ACEI and ARB are very influential on the final outcome because both drugs have anti remodeling induced heart muscle due to the blockade of RAS-related effects of angiotensin II on blood pressure, and systemic hemodynamic and inflammatory markers cardial.[5]

The use of spironolactone is also quite important because there is a study of the role of left ventricular hypertrophy regression. Hyperaldosteronism can increase the incidence of resistant hypertension thereby increasing blood pressure induced left ventricular hypertrophy. Spironolactone is a mineralocorticoid receptor antagonist can control blood pressure and reduce left ventricular hypertrophy, but in this study received spironolactone 25-50 mg daily with optimal doses of thiazide diuretics.[14]

The use of beta blockers, CCB, and furosemide also do not have a significant difference so it can be concluded that all these drugs do not affect the final outcome of this study. The final results of this study showed that consistent with the hypothesis that there is a statistically significant difference using the Mann-Whitney test mean NT proBNP levels between the two groups of subjects (p=0.00). Kolmogorov-Smirnov test showed that the data distribution is not normal. The results obtained from the some of the data from the hypertensive with left ventricular hypertrophy with NT proBNP levels in a number of normal and hypertensive group without left ventricular hypertrophy who have high levels of NT proBNP.

The weakness in this study is a research method that is cross-sectional so it has limitations in determining the levels of NT proBNP correlation with hypertension and left ventricular hypertrophy.

CONCLUSION

There were significant differences in levels of N-terminal proBrain Natriuretic Peptide (NT proBNP) in hypertensive patients without left ventricular hypertrophy and hypertensive patients with left ventricular hypertrophy.

Need to do more research on the N-terminal proBrain Natriuretic Peptide (NT proBNP) with left ventricular hypertrophy so it can be determined the cut-off point for the detection of left ventricular hypertrophy.

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