International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

Bisoprolol Reduced Left Ventricular Hypertrophy in Hypertensive Patients with Gln27Gln (wildtype) β2-Adrenergic Receptor Receiving Angiotensin II Receptor Blocker (ARB)

Mohammad Afies Sjughiarto[a], Mohammad Saifur Rohman[b], YF Galuh Retno A[c], Lenny Kartika Sari[d], Lina Haryati[e], Diah Kristianisah Rahayu[f], Febbi Yustiti Aksari[g], Defi Amelia[g]

[a,b]*Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Brawijaya/ Dr. Saiful Anwar General Hospital, Jaksa Agung Suprapto No.2, Malang, 65112, East Java, Indonesia*

[a]*Email: mc16afiez@gmail.com*

[b]*Email: ippoenk@yahoo.com*

Abstract

Recent evidence has been known that the Glu27 β2AR variant is strongly associated with cardiac hypertrophy in hypertension. Angiotensin II receptor blocker (ARB) and beta-blocker may suppress the catecholamine hypertrophic response to regress left ventricular (LV)-mass in hypertensive patients with β2-AR Gln27Glu polymorphism. The study objective is to determine whether the β2AR polymorphism Gln27Glu or wildtype Gln27Gln was associated with regression of LV-mass during ARB-based antihypertensive treatment or on beta blocker was added to ARBs. With prospective cohort study, 39 patients by inclusion criteria (male, newly diagnosed hypertension or no taking antihypertensive medication more than 2 weeks, age 30-75 years, Asian race) underwent 24- hours Ambulatory Blood Pressure Monitoring, echocardiography examination to assess left ventricular hypertrophy (LVH) before and after 6 months of ARB-based antihypertensive and optimized a regimens based on office blood pressure.

---

* Corresponding author.

Genotype was examined using Restriction Fragment Length Polymorphism analysis. Among hypertensive patients and LVH, the Gln27Gln was found in 84.6% and 81.25%, respectively. In the LVH patients with Gln27Gln genotype, 24 hours systolic and diastolic blood pressure decreased, 11 mmHg (p = 0.028) and 8 mmHg (0.015), respectively and the mean reduction of LVMi came to 59 gr/m^2 (p =0.03) and LV-mass came to 106 gr (p=0.02) after 6 months of ARB-based treatment while Gln2Glu showed significant reductions in regional wall thickness (RWT), indicate a deterioration towards eccentric hypertrophy. Adding beta-blocker to ARBs in the Gln27Gln after 6 months revealed significant decreased in LVMI from 137.11±37.58 to 72.56±28.59(p=0.011) and in LVMass from 243.22±72.69 to 141.22±36.87 (p = 0.01) but not in Valsartan nor Telmisartan group.

Six month treatment with ARB-based antihypertensive significantly decreased blood pressure and regress ventricular mass in LVH with Gln27Gln genotype and addition of beta-blocker to ARBs may produced a significant regression of LVH compared to ARB alone.

Keywords: β-Adrenergic receptors; polymorphism; left ventricular hypertrophy; angiotensin II receptors blocker.

1. Introduction

Left ventricular hypertrophy (LVH) is one of the major manifestations of cardiovascular damage due to hypertension and increased risk of cardiovascular events [1]. The prevalence of LVH due to hypertension based on echocardiography is about 36% [2]. Ching and his colleagues in [3] reported the prevalence of LVH in Malaysia with echocardiography examination is about 24% in uncomplicated primary hypertensive patients. Based on the Framingham Heart Study [4], hypertension contributed heart failure of 39% in men, and 59% in women, while data in Indonesia, hypertension contribute heart failure of 54.4%.

The authors in [4,5] noted that the main factors of LVH consists a hemodynamic factors including high pressure and non hemodynamic factors including humoral mechanism, duration of hypertension, demographic factors, comorbid factors, pharmacological therapy, cellular and molecular genomic expression, growth factors, and interstitial alteration. Anand in [5] noted LVH indicates that the remodeling process is regulated by mechanical, genetic and humoral factors.

Yuan and his colleagues in [6] noted that genetic polymorphism affects the occurrence of LVH by remodeling in hypertension. Bleumink and his colleagues in [7] noted that several studies have demonstrated that remodeling and pharmacological therapy response to left ventricular period by gene polymorphism from RAA system receptors and adrenergic beta receptors. Iaccarino and his colleagues in [8] investigated the effects of Beta-2 receptor polymorphism Adrenergic (β2-AR) to cardiac hypertrophy in hypertensive patients with glutamic acid polymorphism at position 27 (Glu27). The presence of Glu27 polymorphism related with a high risk of LVH compared with patients with Glutamine allele at position 27 (Gln27). In another study, Iaccarino et al. in [9,10] reported that antihypertensive effect on LVH regression level showed a greater regression of ACE inhibitors (enalapril) than with beta blockers (Atenolol). Iaccarino and his colleagues in [10] revealed that their study

showed a decrease in blood pressure can reduce sympathetic discharge overall and provide further benefits to LVH regression.

Wagenaar in [11] noated that the angiotensin II receptor antagonist (ARB) is one class of antihypertensive drugs that block an angiotensin II type I receptor on the cascade of the RAA system and has been shown to effectively lower left ventricular mass index (LVMI) on LVH. Alwi in [12] noted that LIFE Study (Losartan Intervention for Endpoint Reduction of hypertension) and VALUE (The Valsartan Antihypertensive Long Term Use Evaluation) are two major studies showing evidence of the effectiveness of the ARB regimen as an antihypertensive regimen that has a cardiovascular protective effect.

However, until now there are no research on the use of ARBs in order to know the effect of LVH regression on hypertensive patients with Glutamine allele polymorphism replaced by glutamic acid at position 27 (Gln27Glu) at β2-AR receptors. Therefore, the researchers are interested to know the LVH regression response to ARB - based antihypertensive therapy between the Gln27Gln genotype and Gln27Glu receptor polymorphism β2-AR in hypertensive patients at Saiful Anwar General Hospital (RSSA) Malang.

2. Materials and Methods

This was pretest-posttest prospective study. We screened of 39 patients who met any one of the following the inclusion and exclusion criteria (inclusion criteria included male patients aged 30-75 years, newly diagnosed hypertensive patients or hypertensive but not known to take medication for 2 weeks or more, hypertension according to JNC-7 blood pressure Systolic≥140 mmHg and/or 90 mmHg diastolic pressure; exclusion criteria included secondary hypertension, have comorbidities with cardiovascular complications (diabetes mellitus, pulmonary hypertension, lung disease with heart complications, congestive heart failure, coronary heart disease, stroke, renal failure, liver function impairment), contraindicated with ARB, inchronic therapy of corticosteroid and NSAID, known to be drug allergies; Drop-out if the patients who has followed the research process were not obedient to take medication or stop taking medicine by himself, not because of any side effects or allergies. All patients underwent a 24-hour Ambulatory Blood Pressure Monitoring (ABPM) procedure, echocardiogram examination to assess LVH with M-mode calculated based on the American Society of Echocardiograph (LVmass> 224 gram; LVMi> 115 gram/m2; RWT> 0.42). Both of studies will be evaluated at 6 months after ARB-based antihypertensive therapy. During follow-up, antihypertensives therapy would be optimalized by increasing ARB doses and/or adding other antihypertensive based on blood pressure during control. Genotype Gln27Gln and Gln27Glu receptor β2-AR was examined using Restriction Fragment Length Polymorphism (RFLP) analysis with Fnu4HI enzyme. This research was conducted at Malang Saiful Anwar Hospital and Molecular Biology Laboratory Faculty of Mathematics and Natural Sciences Brawijaya University from 1st January 2014 until June 2017. The descriptive statistical analysis was presented in table, diagram and percentage. Comparative analysis was used to assess the difference in left ventricular mass changes between the two genotypes in LVH patients before and after ARB-based antihypertensive therapy and the difference in left ventricular mass changes between ARBs added with beta-blockers versus ARB alone between the two genotypes in LVH patients. The research protocol has been approved by Medical Research Ethics Committee of Faculty of medicine, University of Brawijaya.

3. Result

3.1 Characteristics of Research Subjects

From 1st January 2014 until June 2017, total of 39 male hypertensive patients who met inclusion and exclusion criteria, had been established as a research subject and successfully completed the research for 6 months. The population of this study were divided into 2 goups by genotype, group Gln27Gln (n = 33) and Gln27Glu group (n = 6) with the mean age of patients was 56.4 ± 7.84 years. Basic characteristics of research subjects (table 1) included duration of hypertension, basal mass index (BMI), systolic blood pressure (BP), diastolic BP, left ventricular septal wall thickness (LVSWT), left ventricular posterior wall (LVPW), left ventricular mass index (LVMi), left ventricular mass (LVmass) and relative wall thickness (RWT) showed no significant difference between 2 groups.

Table 1: Basic Characteristics of Research Subjects

Parameter Subject	Gln/Gln (n=33)	Gln27Glu(n=6)	P value
Age (y)	55.97 ± 10.89	58.83 ± 4.79	0.585
Duration of Hypertension(y)	6.19 ± 5.27	7.60 ± 10.71	0.876
BMI (kg/m^2)	25.67 ± 4.22	26.59 ± 4.92	0.688
SBP 24 hours (mmHg)	141.79 ± 16.64	134.88 ± 10.20	0.335
DBP 24 hours (mmHg)	88.66 ± 12.74	89.37 ± 8.43	0.898
LV ST (mm)	1.19 ± 0.33	1.29 ± 0.35	0.447
LV PWT (mm)	1.22 ± 0.27	1.21 ± 0.27	0.953
LVMi (g/m^2)	118.91 ± 50.51	118.83 ± 41.51	0.846
LVMass (gr)	208.30 ± 88.13	211.33 ± 74.91	0.835
RWT (%)	0.56 ± 0.17	0.55 ± 0.12	0.846

3.2 Analysis Variable Research

3.2.1 Regression Variables Before and After ARB-Based Therapies in LVH Groups between Two Genotypes of the β2-Adrenergic Receptors

Among the 39 selected samples, 16 samples met the LVH criteria based on echocardiographic examination with LVMi more than 115 gram/m^2 and/or LVMass more than 224 gram. The entire sample completed the study according to the specified duration of 6 months. Most of the parameters of the two genotypes showed average mean impairment after ARB-based therapy followed for 6 months (Table 2). In the Gln27Gln (wild type) group, there was a significant difference after 6 months of ARB-based antihypertensive therapy on the 24-hour systolic blood pressure (24-hour SBP) variable, 24-hour diastolic blood pressure variable (24-hour DBP), LVMi (p = 0.038) and LVMass (p = 0.027). (Figure 1). While in the Gln27Glu group, the RWT value after 6 months had a significant difference with the p = 0.010. (Figure 2)

Table 2: Parameters of Regression Variables Before and After ARB-Based Therapies in LVH Groups with Genotype of the ß2-Adrenergic Receptor

Parameter of Regression Variabel	**ARB-based treatment**			
	Gln/Gln (n= 13)		Gln27Glu (n=3)	
	Before treatment	After 6 m follow-up	Before treatment	After 6 m follow-up
BMI (kg/m^2)	24.94 ± 3.84	24.45 ± 3.88	26.31 ± 4.05	26.81 ± 3.80
SBP 24h (mmHg)	150.46 ± 16.25	139.52 ± 14.08*	140.90 ± 6.39	145.67 ± 19.39
DBP 24h (mmHg)	92.23 ± 14.15	84.26 ± 9.02*	92.73 ± 10.89	93.83 ± 10.85
LVMi (g/m^2)	169.00 ± 42.98	110.61 ± 57.03*	153.33 ± 15.63	158.67 ± 99.12
LVMass	293.08 ± 76.40	187.46 ± 70.48*	274.00 ± 43.48	166.67 ± 43.59
RWT (%)	0.55 ± 0.12	0.51 ± 0.20	0.63 ± 0.08	0.50 ± 0.12*

*p<0,05

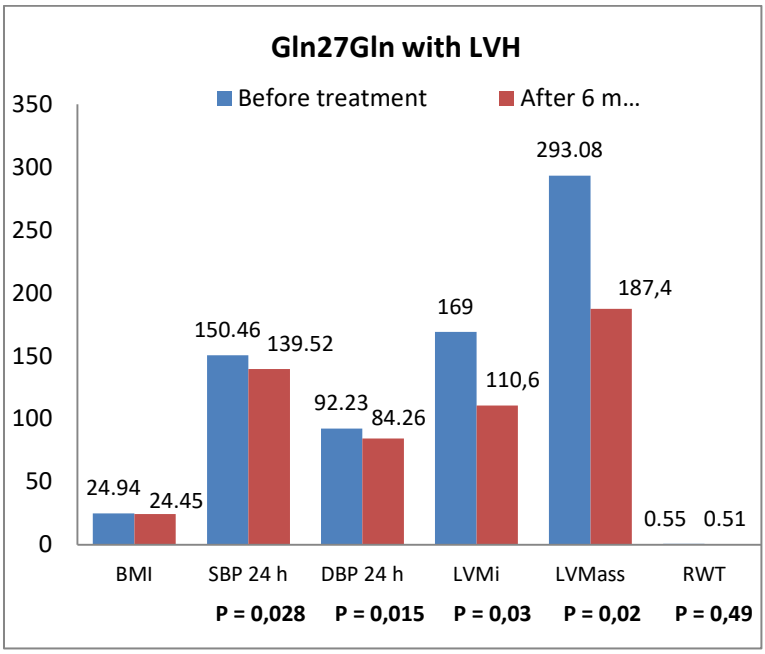

Figure 1: Alteration of Parameter Value of Regression Variables Before and After ARB-Based Therapies in LVH Group with the ß2-Adrenergic Receptors Gln27Gln

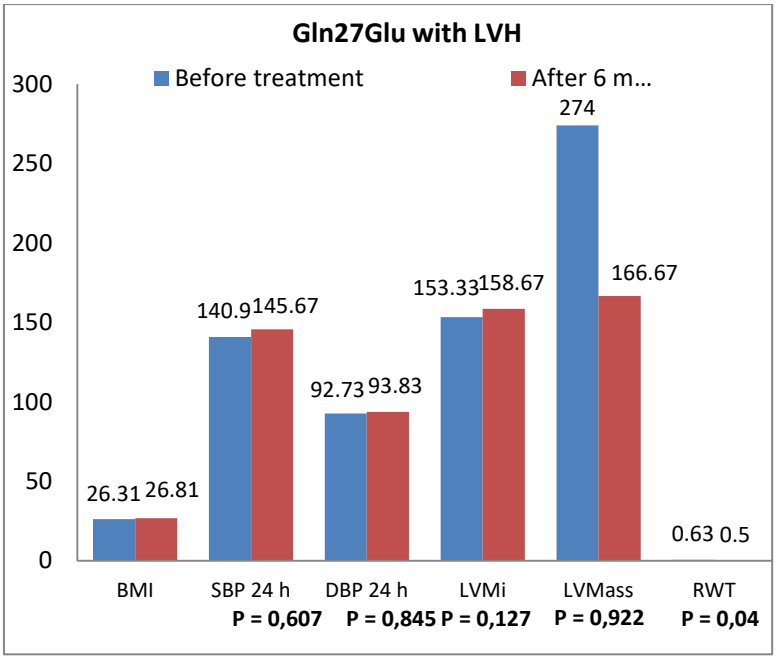

Figure 2: Alteration of Parameter Value of Regression Variables Before and After ARB-Based Therapy in LVH Group with Adrenergic Receptor β2-Gln27Glu

3.2.2 Role of Therapy Based on Angiotensin II Receptor Blocker (ARB) and Combination with Beta-Blocker on Left Ventricular Hypertrophy Regression (LVH)

The ARB effect on regression variable parameters (LVMi, LVMass, and RWT) was divided into three groups categories:

Telmisartan, Valsartan and adding beta-blocker to ARB (Telmisartan or Valsartan) group, while regression changes of LVH divided into Gln27Gln and Gln27Glu groups.

The results of the analysis (Table 3), in Gln27Gln group, the administration of ARBs both Telmisartan and Valsartan showed no significant changes, but the mean value of Telmisartan showed a larger LVMi and LVMass reduction effect compared to Valsartan.

Telmisartan group revealed regression effect of LVMi and LVMass before and after 6 months therapy respectively 146,75 ± 40,14 to 52,75 ± 26,39 (0,068) and 272,25 ± 82,85 to 126,00 ± 24.62 (0.068) while the Valsartan group revealed the decreases of LVMi from 129.40 ± 38.06 to 88.40 ± 20.16 (p = 0.08) and LVMass from 220.00 ± 62.49 to 153.40 ± 42.99 (p = 0.08).

ARB and Beta-blocker combination group showed significant decreased of LVMI after 6 months administration from 137.11 ± 37.58 to 72.56 ± 28.59 (p = 0.011) and LVMass from 243.22 ± 72, 69 to 141.22 ± 36.87 (p = 0.01). In the LVH group Gln27Glu, there was no significant difference of all regression parameters studied, neither ARB Telmisartan, Valsartan group nor ARB and Beta-blocker combination group.

Table 3: Regresion of LVH based on Type of Angiotensin II Receptor Blocker (ARB)

LVH regression on Telmisartan Administration (n=6)						
	Gln27Gln			Gln27Glu		
Variable	Before therapy	After 6mo therapy	P	Before therapy	After 6mo therapy	P
SBP	142,15 ± 13,68	136,83 ± 17,53	0,465	137,80 ± 14,57	144,9 ± 32,24	0,655
DBP	84,78 ± 6,60	83,05 ± 10,32	0,715	94,95 ± 14,35	94,15 ± 30,19	0,655
LVMI	146,75 ± 40,14	52,75 ± 26,39	0,068	124,00 ± 21,21	83,00 ± 4,24	0,180
LVMass	272,25 ± 82,85	126,00 ± 24,62	0,068	212,50 ± 45,96	142,50 ± 0,71	0,180
RWT	0,46 ± 0,08	0,40 ± 0,08	0,273	0,54 ± 0,05	0,40 ± 0,06	0,180
LVH regression on Valsartan Administration (n=5)						
SBP	156,2 ± 17,92	142,96 ± 17,89	0,223	n.a	n.a	n.a
DBP	98,86 ± 13,60	85,26 ± 10,47	0,225	n.a	n.a	n.a
LVMI	129,40 ± 38,06	88,40 ± 20,16	0,080	n.a	n.a	n.a
LVMass	220,00 ± 62,49	153,40 ± 42,99	0,080	n.a	n.a	n.a
RWT	0,61 ± 0,21	0,47 ± 0,26	0,345	n.a	n.a	n.a
LVH regression on Beta-Blocker adding to ARB (n = 11)						
SBP	149,96 ± 16,90	140,23 ± 16,9	0,260	137,80 ± 14,57	144,90 ± 32,24	0,655
DBP	92,60 ± 12,80	84,28 ± 9,80	0,173	94,95 ± 14,35	94,15 ± 30,19	0,655
LVMI	137,11 ± 37,58	72,56 ± 28,59	0,011	124,00 ± 21,21	83,00 ± 4,24	0,180
LVMass	243,22 ± 72,69	141,22 ± 36,87	0,011	212,50 ± 45,96	142,5 ± 0,71	0,180
RWT	0,54 ± 0,17	0,44 ± 0,19	0,154	0,54 ± 0,05	0,40 ± 0,06	0,180

4. Discussion

4.1 General data

Iaccarino and his colleagues in [10] noted that ß2-Adrenergic (ß2-AR) gene is a highly polymorphic, and has a variant at positions 16 and 27 that alter the signaling regulation of receptors. During the evolution of genes, the proximity of these two mutations has created an imbalance which causes the patient has a hidden Glu27 (harboring) by displaying Gly16 in most cases. The hypertensive patients in this study showed that the β2-AR gene at position 27 had the genotype distribution Gln27Gln in 33 patients (84.6%) and the Gln27Glu genotype in 6 patients (15.4%). The deviation of the Hardy-Weinberg balance of the ß2-AR Gln27Glu gene polymorphism from previous studies showed varying distribution.

Ge and his colleagues in [13] noted that genotype frequencies of Gln27Gln, Gln27Glu, and Glu27Glu amongnormotensive patients in South Chinawere were 84%, 14.1% and 1.9%, respectively dn in China Han North, the genotype frequencies of ß2-AR polymorphism Gln/Gln, Gln/Glu and Glu/Glu in hypertensive

patients were 90.6%, 7.8% 1.6%, respectively. Komara and his colleagues in [14] reported that the genotype frequencies of β2-AR polymorphism in Malaysia was differences between hypertensive patients compared with normotensive in Gln27Gln, Gln27Glu, Glu27Glu. The frequencies were, 41.1%, 50% and 1.9% compared to 77.5% , 20.6% and 1.9%, respectively.

There was no significant difference in patients with basic characteristic between genotype Gln27Gln compared with Gln27Glu. There was no significant differences systolic and diastolic blood pressures between two genotypes but patients with Gln27Gln showed a higher measure of systolic blood pressure than diastolic blood pressure. There was also no significant differences in LVMi, LVMass and RWT. Iacarrino and his colleagues in [10] reported there was no significant differences in blood pressure characteristics either genotype genotype Gln27Gln or Gln27Glu, in contrast, LVMi parameters showed a significant difference between Gln27Glu and Glu27Glu but not significantly different in Gln27Gln. Invivo and invitro studies showed that the role of Glu27 causes an overreaction to catecholamines. Glu27 ß2-AR has been reported to induce agonist resistance to agonist-promoted down-regulation in vitro and to increase agonists responsiveness invivo. Some other reports in the literature contradict these findings showing that other ßAR-dependent physiologic responses are depressed in the presence of the Glu27 polymorphism in vivo. Yuan in [6] reported that patients with Glu27Gln had significantly higher LVMi and LVmass by electrocardiogram than genotype Gln27Gln.

4.2 Relation between Genotype of ß2-Adrenergic Gln27Glu to Left Ventricular Hypertrophy Regression

From 16 samples who complied LVH criteria, this study showed that 13 patients with Gln27Gln genotype had a significant difference in SBP 24-hour, DBP 24-hour , LVMi and LVMass, whereas the RWT parameter showed no significant difference on ARB therapy between before and after 6 months follow up. 24-hours blood pressure, systolic and diastolic, showed a decreased of 11 mmHg ($p = 0.028$) and 8 mmHg (0.015) respectively, after 6 months of ARB-based therapy. The LVMi values in the Gln27Gln group before ARB-based therapy wer 169 ± 42.98 g/m^2 with a reduction of 59 gr/m^2 ($p = 0.03$) after therapy and the LV Mass was 293 ± 76.4 gr of with a reduction of 106 g after therapy ($p = 0.02$). Gln27Gln genotype group showed improvement of LVMi and LV Mass during the 6 month follow up treatment. RWT was decreased despite insignificantly. The direction of the change quadrant from LVH to concentric remodeling suggests ARB-based antihypertensive administration might have an improvement effect by regressing left ventricular mass and inhibiting hypertrophy.

In a randomized, double-blind trial conducted by Thu¨rmann and his colleagues in [15] reported that 69 predominantly previous untreated hypertensive patients with echocardiographically proven LVH received either valsartan or atenolol for 8 months. After 8 months therapy with valsartan (n=29), LVMI decreased from 127±23 to 106±25 g/m^2 ($P<0.0001$ versus baseline). Under atenolol (n=29), LVMI decreased to a smaller extent, from 127±25 to 117±27 g/m^2 ($P=0.0082$ versus baseline). The mean reduction of LVMI was 21 g /m^2 under valsartan and only to 10 g/m^2 under atenolol. Baseline mean blood pressure value was 163 ± 12/101±6 mmHg before treatment with valsartan and decreased to 146 ± 13/90 ± 7 mmHg after 8 months of treatment. Iaccarino and his colleagues in [10] reported that an administration of antihypertensive drug enalapril in patients with LVH in allele group 27 (n = 107) for 2 years of follow-up showed a significant decrease in systolic and diastolic blood pressure from 162.9±20.6 and 101.2±9.3 mmHg before therapy to 137.4±15.4 and 83.6±9.3 mmHg after therapy

and LVMi decreased from 138.9±18.5 g/m^2 to 135.3±17.5 g/m^2.

Contrast to the LVH group with Gln27Glu polymorphism, there was no difference between SBP and DBP 24 hours, LVMi and LV Mass but had a significant decrease in RWT parameters. After 6 months therapy, 24-hours ABPM average remained elevated and uncontrolled despite received ARB-based antihypertensive therapy. Significant decrease in RWT exhibited progressive worsening towards eccentric hypertrophy. Gln27Glu polymorphism in the LVH group patients showed a tendency to treatment resistance. Cipolletta in [9] noted that combinations of SNP polymorphisms from other genotypes on β2-AR receptors might explain why a treatment resistance occur. Among the β2-AR variants, there are 3 polymorphisms that cause amino acid sequence and signal transduction changes. Arg16Gly is associated with increased agonists induces downregulation, Gln27Glu inhibits agonist and induces downregulation, and Thr164Ile inhibit receptor bonds affinity with ligands thus decrease G-protein interactions of ß2-AR.

Cipolletta in [9] noted that the role of ß1-AR receptor polymorphisms is compared with receptors ß2-AR. It is known that the β1-AR receptor is more dominant than the ß2-AR receptor in the heart. However, the long exposure of agonists cause decrease cellular receptors (down-regulation) through independent activation of degradation mechanisms (ubiquitination). To restore the complement of ß2-AR membrane, it requires the transcription level of the ß2-AR gene and post-translational conversion of mRNA into protein and PI3K activation, result in upregulation of ß2-AR. This data explained the duration of hypertension in Gln27Glu group was 7.6±10.71 years. This suggested that the duration of hypertension indicates a chronic condition of agonist exposure so the polymorphism of the ß-AR receptor was highly feasible.

Yuan and his colleagues in [6] evaluated the genetic co-operation between the β1-AR and β2-AR receptor polymorphisms. That study showed patients with Ser49Gly/Glu27Gln had large LVMi (169 ± 20.7) compared with other combinations (Ser49Ser/Gln27Gln, Ser49Ser/Glu27Gln, Ser49Gly/Gln27Gln, Gly49Gly/Gln27Gln). Another explanation that might support the results of this study was the Arg16Arg/Gln27Glu haplotype showed a high LVMi compared to other haplotypes.

4.3 Angiotensin II Reseptor Blocker (ARB)-Based Therapy Response Differences for Left Ventricular Hypertrophy in Hipertensive Patients with β2-Adrenergic Gln27Glu and Gln27Gln Receptors Polymorphism

ARB-based and beta-blocker combination therapy in Gln27Gln (wildtype) group showed significant changes in LVMI. After 6 months ARB and beta blockers combination therapy, LVMI decreased from 137.11 ± 37.58 to 72.56 ± 28.59 ($p = 0.011$) and the LVMass decreased from 243.22 ± 72.69 to 141.22 ± 36 ($p = 0.01$). This significant decrease of LVMI and LV Mass changes indicated that the combination between ARB and beta-blocker classes therapy had improvement effect with decreased left ventricular hypertrophy mass compared to the single agent ARB therapy. The rationale of this effect was the role of beta-blockers in enhancing the inhibitory effects of both hemodynamic and neurohormonal factors. Angiotensin II receptor blocker (ARB) inhibited worsening of the heart through AT1 receptor inhibition path and maintained the cardioprotective effect of Angiotensin II with AT2 receptor. With combination of beta-blocker, bond between β-AR receptors will increased protective effect in both systemic and cardiomyocyte level.

In a randomized double-blind trial conducted by Thu¨rmann and his colleagues in [15] reported that 69 patients with untreated hypertension with LVH proved by echocardiography, left ventricular mass index (LVMI) > 134 g/m^2 in men and> 110 g/m^2 in women and/or end-diastolic septal thickness> 12 mm, consumed angiotensin II receptor blockers valsartan and atenolol for 8 months. Echocardiographic data of 58 patients were taken after 8 months therapy. In valsartan group (n = 29), the LVMI decreased from 127 ± 23 to 106 ± 25 g/m^2 (ratio [R] = 0.83; 95% CI, 0.79-0.87; P,0.0001 versus baseline). While in atenolol group (n = 29), LVMI decreased slightly, from 127 ± 25 to 117 ± 27 g/m^2 (R = 0.92; 95% CI, 0.86 -0.98; P50.0082 versus baseline). The mean LVMI reduction was about 21 g/m^2 in valsartan group and only 10 g/m^2 in atenolol group (R=0.91; 90% CI, 0.85-0.97 versus atenolol).[15]

The results of this study indicated that the role of ARB in both genotypes showed no significant difference, but when combined with beta-blocker there was a significant decrease in Gln27Gln genotype group. Although SBP and DBP decrease didn't show any significant difference as a hemodynamic factor, the combination ARB and beta-blocker therapy might had a synergistic effect in inhibiting and decreasing left ventricular mass in LVH through non hemodynamic factor pathways. It was well known that LVH was a multifactorial condition that affected by the hemodynamic, neurohormonal and genetic relationships effects. Blood pressure accounted for no more than 25% of the overall LVMI variation.10 After separation of drug types and combinations, This study showed that the role of ARBs alone did not provide regression effect on LVH mass. But combination therapy of ARB and beta-blockers might had synergistic effects that could prevent and decrease LVH and finally decrease the cardiac event number.

5. Conclusion

ARB-based antihypertensive therapy for 6 months shows significant differences in left ventricular mass regression in hypertensive patients with the Gln27Gln genotype of the ß2-Adrenergic receptor. In contrast, hypertensive patients with Gln27Glu polymorphism shows ARB-based antihypertensive therapy do not show significant regression effect on LVH but there is significant change in relative wall thickness (RWT) that may indicate a change towards eccentric hypertrophy.

ARBs is known to have a better regression effect compared to other antihypertensives drugs, especially beta-blockers. Monotherapy with ARB for 6 months do not give significant LVH mass regression effects for both Telmisartan and Valsartan groups. However, addition of beta blockers to ARB therapy shows significant regression in LVH mass. This suggests that the combination of these two agents provides a better regression effect than single therapy with ARB agents.

References

[1]. Kaplan NM. Kaplan's Clinical Hypertension. Philadelphia: Lippincott Williams & Wilkins; 2006.

[2]. Cuspidi C, Sala C, Negri F, Mancia G, Morganti4 A. Prevalence of left-ventricular hypertrophy in hypertension: an updated review of echocardiographic studies. Journal of Human Hypertension. 2012; 26:343-349.

[3]. Ching SM CY, Wan Azman WA. Prevalence and Determinants of Left Ventricular Hypertrophy in Hypertensive Patients at a Primary Care Clinic. Malaysian Family Physician. 2012; 7.

[4]. Prawisanthi GAR, Pratanu I. Hipertensi pada Gagal Jantung. In: Pikir BS, Aminuddin M, Subagjo A, Dharmadjati BB, Suryawan IGR, Eko JN, editors. Hipertensi Manajemen Komprehensif. Surabaya: Pusat Penerbitan dan Percetakan Unair (AUP); 2012.

[5]. Anand IS, Florea VG. Alterations in Ventricular Structure:Role of Left Ventricular Remodeling. In: Mann DL, editor. Heart Failure A Companion to Braunwald's Heart Disease. Missouri: Elsiever Saunders; 2011.

[6]. Yuan M, Ohishi M, Ito N, Sugimoto K, Takagi T, Terai M, et al. Genetic Influences of Beta Adrenoceptor Polymorphisms on Arterial Functional Changes and Cardiac Remodeling in Hypertensive Patients. Hypertens Res. 2006; 29:875-881.

[7]. Bleumink GlS, Schut AFC, Sturkenboom MCJM, Deckers JW, Duijn CMv, Bruno H.Ch. Stricker P. Genetic polymorphisms and heart failure. Genet Med. 2004; 6.

[8]. Cipolletta E, Luca GD, Carillo AL, Annunziata R, Trimarco B, Iaccarino G. β2 Adrenergic Receptor Polymorphisms and Treatment-Outcomes in Cardiovascular Diseases. International Journal of Cardiovascular Research. 2013; 2(1).

[9]. Cipolletta E, Carillo A, Roberto Annunziata BT, Franco A, Iaccarino G. The impact of 2 adrenergic receptor polymorphisms on the outcomes in cardiovascular diseases. Cardiogenetics. 2014; 4:4661.

[10]. Guido Iaccarino, Raffaele Izzo, Valentina Trimarco, Ersilia Cipolletta, Francesca Lanni, Daniela Sorriento, et al. β2-Adrenergic receptor polymorphisms and treatment-induced regression of left ventricular hypertrophy in hypertension. Clinical Pharmacology & Therapeutics. 2006; (80):633-645.

[11]. Wagenaar LJ. Angiotensin receptors in the cardiovascular system. Canadian Journal of Cardiology 2002; 18(12):1331-9.

[12]. Alwi I. Tatalaksana Holistik Penyakit Kardiovaskular. Jakarta: Interna Publishing; 2012.

[13]. Ge D, Huang J, J.He, B.Li, Duan X, Chen R, et al. β2-Adrenergic Receptor Gene Variations Associated with Stage-2 Hypertension in Northern Han Chinese. Annals of Human Genetics. 2005; 69.

[14]. Komara M, Vasudevan R, Ismail P, Bakar SA, Pishva SR, Heidari F. Association of beta 2 adrenoceptor gene polymorphisms in Malaysian hypertensive subjects. Genet Mol Res. 2014; 13(2):2939-48.

[15]. Thu¨rmann PA, Kenedi P, Schmidt A, Harder S, Rietbrock N. Influence of the Angiotensin II Antagonist Valsartan on Left Ventricular Hypertrophy in Patients With Essential Hypertension. Circulation. . 1998; 98:2037-2042.