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Structural and Functional Impact of Adrenoceptor Beta-1 Gene Polymorphism in Patients with Hypertrophic Cardiomyopathy and Response to Beta-Blocker Therapy

ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is a genetically inherited cardiac disorder with diverse clinical presentations. Adrenergic activity, primarily mediated through beta-adrenoceptors, plays a central role in the clinical course of HCM. Adrenergic stimulation increases cardiac contractility and heart rate through beta-1 adrenoceptor activation. Beta-blocker drugs are recommended as the primary treatment for symptomatic HCM patients to mitigate these effects.

Methods: This prospective study aimed to investigate the impact of common ADRB-1 gene polymorphisms, specifically serine–glycine at position 49 and arginine–glycine at position 389, on the clinical and structural aspects of HCM. Additionally, the study explored the association between these genetic variations and the response to beta-blocker therapy in HCM patients.

Results: A cohort of 147 HCM patients was enrolled, and comprehensive assessments were performed. The findings revealed that the Ser49Gly polymorphism significantly influenced ventricular ectopic beats, with beta-blocker therapy effectively reducing them in Ser49 homozygous patients. Moreover, natriuretic peptide levels decreased, particularly in Ser49 homozygotes, indicating improved cardiac function. Left ventricular outflow obstruction, a hallmark of HCM, was also reduced following beta-blocker treatment in all patient groups. In contrast, the Arg389Gly polymorphism did not significantly impact baseline parameters or beta-blocker response.

Conclusion: These results emphasize the role of the Ser49Gly polymorphism in the ADRB-1 gene in shaping the clinical course and response to beta-blocker therapy in HCM patients. This insight may enable a more personalized approach to managing HCM by considering genetic factors in treatment decisions. Further research with larger populations and longer follow-up periods is needed to confirm and expand upon these findings.

Keywords: Adrenoceptor-1 gene polymorphism, genetics, hypertrophic cardiomyopathy

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is the most common genetically transmitted cardiac disorder, affecting about 1/500 of individuals of the population.[1] While patients may be symptom free in the early stages of the disease, most patients suffer from exercise intolerance and shortness of breath as the disease progresses. Impaired left ventricular filling and dynamic left ventricular outflow obstruction are important mechanisms underlying symptoms in HCM and both can be augmented by myocardial hypercontractility. Therefore, adrenergic activity plays a central role in the clinical course of HCM by increasing cardiac contractility and the heart rate through B1 adrenoceptor activation. Moreover, adrenergic activity can also cause structural changes in the myocardium; previous studies showed accelerated myocyte necrosis and cardiac fibrosis by isoproterenol through beta adrenergic stimulation.[2] Similarly, renin synthesis in response to B1 adrenoceptor activity activates the renin–angiotensin–aldosterone system, which causes remodeling of the heart chambers along with myocardial fibrosis. Considering the aforementioned potential effects of the adrenergic activation

ORIGINAL INVESTIGATION

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in the pathophysiology of HCM, blockage of the adrenergic activity is an essential therapeutic target in patients with HCM and the current guidelines recommend beta-blocker drugs as the first-line medical therapy in symptomatic patients with HCM, which mainly affect via reducing myocardial contractility and the heart rate.[1,3] However, there may be substantial variability in symptom relief in response to beta blocker therapy among HCM patients and some patients remain unresponsive to beta-blockers.[4] While the causes of this variability of response to beta blockers are not clearly understood, one potential mechanism may reside in the polymorphism of beta-adrenoceptors. There are previously demonstrated single nucleotide polymorphisms (SNP) of the beta-adrenoceptor coding genes (ADRB-1) which alter the activation of beta-receptors via adrenergic stimulus.[5] The most commonly studied SNPs at the adrenoceptor gene beta-1 (ADRB-1) are serine–glycine polymorphism at 49. position and arginine–glycine polymorphism at 389. position. Several studies demonstrated that these SNPs have clinical impact on drug responsiveness and disease progression in hypertension and dilated cardiomyopathy patients.[6-9] To the best of our knowledge, there is no study in the literature which investigated the impact of ADRB-1 SNPs on the clinical course of patients with HCM. In this study, our primary aim was to investigate the impact of ADRB-1 gene polymorphism on clinical and structural features of hypertrophic cardiomyopathy. We also searched for the association between ADRB-1 polymorphism and response to beta-blocker therapy in patients with HCM.

METHODS

Study Design

The study was conducted in a university hospital cardiology clinic, which is a tertiary reference center for HCM. Patients who were diagnosed with HCM but naive to medical therapy were prospectively enrolled after informed consent was obtained. The study protocol was following the Declaration of Helsinki and was approved by the Local Ethics Board of our institution (date: August 10, 2018; number: 30330229-604010 2-42266). The diagnosis of HCM was made according to current guidelines; at least 15 mm of thickness at any region of the left ventricle which was not related to the increased afterload.[1,3] Inclusion criteria were as follows: (i) patients with a clear diagnosis of HCM, (ii) patients over 18 years, (iii) patients naive to medical therapy including beta-blockers and calcium channel blockers. Patients were excluded from the study if one of the following were present: (i) already under medical treatment for HCM, (ii) previous septal reduction therapy either via alcohol ablation or surgical myectomy, (iii) refusal for informant consent, (iv) unable to attend regular visits, and (v) having resistant hypertension. Patients' demographic features, family history, functional capacity, heart rate and blood pressures were recorded. The 5-year risk of sudden cardiac death was calculated using the ESC risk calculator during the enrolment and ICD implantation was performed according to current guideline recommendations.[3]

Beta-Blocker Therapy

Following enrolment, metoprolol 25 mg once a day was prescribed to each patient, and dose adjustment was made according to blood pressure and mean heart rate which were derived from 24-hour ambulatory Holter monitoring. The dose of metoprolol was up titrated to achieve symptom free status with a maximum dose of daily 200 mg. Pre-treatment and post-treatment blood pressures, heart rate and functional capacity of the patients were recorded. Functional capacity was defined according to the New York Heart Association (NYHA) classification. Beta-blocker intolerance was defined as symptomatic bradycardia, hypotension, or deterioration of exercise capacity following beta-blocker initiation that required discontinuation of beta-blocker therapy.

Echocardiography

All patients underwent comprehensive echocardiographic evaluation with Philips EPIQ echocardiography machine (Philips, Andover, MA, USA). One of the 2 board-certified cardiologists performed echocardiography and the other one analyzed the data. In case of disagreement, a third senior cardiologist reviewed the data, and a final decision was reached. Maximum wall thickness was measured at the particular left ventricular (LV) segment where the wall thickness is highest. LV ejection fraction was calculated using biplane modified Simpson's method. Left atrial volume was also measured using biplane Simpson's method and indexed to the body surface area. LV longitudinal strain assessment was performed by an automatic border detection program, and manual correction was made when necessary. Systolic anterior motion (SAM) was defined as the motion of the anterior mitral valve leaflet towards the interventricular septum during systole. LV apical aneurysm was diagnosed when obvious akinesia/aneurysm was observed at the LV apex. LV outflow gradient was measured in apical 5-chamber view using pulsed wave Doppler at rest and following Valsalva maneuver.

ECG Evaluation

Patients' initial heart rhythm and rate were determined on a 12 lead ECG. Presence of fragmented QRS which is defined

HIGHLIGHTS

- This study delves into the impact of ADRB-1 gene polymorphism on clinical and structural aspects of HCM. The research is novel as it investigates the association between ADRB-1 SNPs, particularly Ser49Gly polymorphism, and HCM, filling a knowledge gap.
- The study reaffirms the role of beta-blocker therapy as the first-line treatment for symptomatic HCM patients. It shows that beta-blockers effectively reduce heart rate and premature ventricular contractions across different ADRB-1 gene polymorphisms, promoting symptom alleviation in HCM patients.
- The research highlights the beneficial effects of beta-blocker therapy on HCM patients, including a significant decrease in natriuretic peptide levels and LVOT obstruction. These findings contribute to our understanding of the structural and clinical improvements associated with beta-blocker treatment in HCM.

as the presence of notching within the R wave or S wave was recorded. A 24-hour ambulatory ECG Holter monitor was used to monitor heart rate and rhythm and maximum, minimum, and mean heart rate in all the patients. ECG Holter monitoring was performed on every patient during enrolment and at sixth-month visit, and a comparison between these 2 recordings was made to assess the effect of beta-blocker therapy. Ventricular tachycardia was defined as a cardiac rhythm that is originating from the ventricles with a rate of >100 beats/min. Atrial fibrillation was diagnosed when an irregular rhythm with the absence of obvious p waves was seen either on 12-ECG or Holter monitoring. Ventricular extra systole count in 24 hours was recorded.

Genetic Analysis

Single nucleotide polymorphism (SNP) protocol was used for the genetic analyses. To assess polymorphisms in adrenoceptor beta-1 gene rs1801252 (Ser49Gly) and rs1801253 (Arg389Gly), TaqMan System (Applied Biosystems, Life Technologies) Primer ProbMix and qPCR Probes Master (Jena Bioscience, Germany, PCR-360) were used. Two SNPs were evaluated which cause Arginine/Glycine polymorphism at the 389. position and Serine/Glycine polymorphism at the 49. position of adrenoceptor beta-1 gene. Patients were divided into 3 groups according to Arg389Gly polymorphism; Arg389Arg homozygotes, Arg389Gly heterozygotes and Gly389Gly homozygotes. However, due to the lower number Gly49Gly homozygotes, patients were divided into 2 groups according to Ser49Gly polymorphism; Ser49Ser homozygotes constituted group 1, and Ser49Gly and Gly49Gly constituted group 2 (Glycine carriers).

Follow-up

Patients were followed up in a dedicated outpatient clinic. The follow-up visits were done at the end of the first week, first month, and then 3 months after the second visit. Patients' heart rates, blood pressure and response to beta-blocker therapy were recorded to optimize the therapy. However, only the data from the initial encounter and final visits with the patients were included in the statistical analysis.

Statistical Analysis

All statistical analyses were conducted by Statistical Package for the Social Sciences Statistics, version 25.0, for Windows (SPSS Inc., Chicago, Ill, USA) Program. The sample size is defined by effect size, type 1 error, and power of the study with the G-Power Program. Type 1 error was 5%, power of the study was 80%, effect size was calculated by other studies in the literature. The Kolmogorov–Smirnov test was used to analyze the normality of the data. Normally distributed variables were expressed as mean ± SD, while non-normally distributed variables were expressed as median with minimum–maximum value. The categorical variables are presented as percentages. A Chi-square test was used to assess differences in categorical variables between groups. Student's *t*-test or Mann Whitney *U*-test was used to compare unpaired samples as needed. The primary analysis used ANOVA to compare all reported data for parametric variables, whereas the Kruskal–Wallis test was used to compare nonparametric variables between the median value of the survival days. According to the values distribution, paired *t*-test or/and Wilcoxon test is used for the comparison of the same subjects' values before and after treatment with beta-blockers of HC patients. Significance was assumed at a 2-sided $P < .05$.

RESULTS

The study was conducted from September 2018 to May 2021. One hundred ninety-four patients with a working diagnosis of HCM were screened. Patients with resistant hypertension (36 patients), aortic sclerosis (4 patients), Amyloidosis (6 patients), and Fabry disease (1 patient) were excluded during the study and finally, 147 patients were enrolled. The mean follow-up duration was 23 months (6-32 months). Table 1 demonstrates the baseline demographic variables and echocardiographic features of the study population and group statistics according to gender distinctions. The most common presenting symptoms were shortness of breath and palpitations during physical activity (65% and 50% of the study population respectively). Previous episodes of syncope (20.4%) and exercise angina (17%) were the other common symptoms of the patients. The vast majority of the study population demonstrated septal hypertrophic cardiomyopathy (83%). The distribution of HCM variants in the study population was; 83% septal, 11% apical, 3% global, and 3% mid-ventricle. Systolic anterior motion of the mitral valve was detected in 40 patients (27%).

The target dose beta-blocker therapy 200 mg/day was achieved in 92.5% of the study patients. Beta-blocker therapy was not up-titrated or discontinued in 10 patients due to increased exercise intolerance or hypotension.

The risk of sudden cardiac death which is determined using the HCM sudden cardiac death calculator was low (<4%) in 55.8%, intermediate (4%-6%) in 24.5%, and high (>6%) in 19.7% of the study population.

Arginin389Glycine Polymorphism

Patients were divided into 3 groups according to Arginin389Glycine gene polymorphism; Arg389 homozygotes (n= 43; 29%), Arg389Glycine heterozygotes (n= 42; 29%) and Glycine389 Homozygotes (n= 62; 42%).

Basal heart rate, rhythm, and blood pressures: The mean heart rate was 79.1 ± 15.5 beats/min in Arg389 homozygotes, 81.7 ± 17.2 beats/min in Arg389Gly heterozygotes, and 83.2 ± 15.7 beats/min in Gly389 homozygotes and there was no significant difference between the groups (Table 2). The incidence of atrial fibrillation and non-sustained ventricular tachycardia were similar between the groups ($P = .495$ and $P = .553$, respectively). There was also no significant difference between groups with respect to 24 hours VES count ($P = .693$). Systolic blood pressures during the enrolment were 145.7 mm Hg for Arg389 homozygotes, 148.4 mm Hg for Arg389Gly heterozygotes and 147.1 mm Hg for Gly389 homozygotes. There was no significant difference between the groups ($P = .905$).

Table 1. Patient's Demographics, Clinical Features, and Group Statistics According to Gender Distinctions

	Total (n = 147)	Male (n = 113)	Female (n = 34)	*P*
Age (mean, years)	49.5 ± 13.1	48.5 ± 13.5	52.7 ± 11.5	.112
Hypertension, n (%)	75 (51)	55 (49)	20 (59)	.299
Diabetes mellitus, n (%)	18 (12)	9 (8)	9 (26)	.004
Hyperlipidemia, n (%)	18 (12)	12 (11)	6 (18)	.273
Coronary artery disease, n (%)	28 (19)	23 (20)	5 (15)	.462
Family history of hypertrophic cardiomyopathy, n (%)	48 (33)	34 (30)	14 (41)	.197
Active smoker, n (%)	60 (41)	55 (49)	5 (15)	<.001
Hypertrophic segment				.606
Septum, n (%)	123 (83)	92 (81)	31 (91)	
Mid-ventricle, n (%)	4 (3)	4 (3)	0 (0)	
Apical, n (%)	16 (11)	14 (12)	2 (6)	
Global, n (%)	4 (3)	3 (2)	1 (3)	
Systolic anterior motion of mitral valve, n (%)	40 (27)	28 (25)	12 (35)	.175
Left ventricular outflow obstruction, n (%)	60 (41)	44 (39)	16 (47)	.398
Left ventricular ejection fraction (mean, %)	60.3 ± 7.4	59.9 ± 7.1	61.7 ± 8.0	.199
Left ventricular global longitudinal strain (mean, %)	−15.3 ± 4.9	−15.5 ± 4.8	−15.3 ± 4.3	.845
Left atrial volume index (mean, mL/m^2)	35.2 ± 13.4	34.2 ± 12.2	38.6 ± 16.5	.162
Ser49Gly				.518
Serine homozygotes	106 (72)	80 (71)	26 (76)	
Glycine carriers	41 (28)	33 (29)	8 (24)	
Gly389Arg				.501
Glycine homozygotes	62 (42)	46 (41)	16 (47)	
Gly389Arg heterozygotes	42 (29)	35 (31)	7 (20)	
Arginine homozygotes	43 (29)	32 (28)	11 (32)	

Table 2. Basal Heart Rate, Rhythm, and Blood Pressure in Arginine389Glycine Polymorphism

	Arg389 Homozygotes	Gly389 Homozygotes	Heterozygotes	*P*
Mean HR	79.1 ± 15.5	83.2 ± 15.7	81.7 ± 17.2	.451
VES count	120 (0-2599)	126 (0-4573)	132 (0-3526)	.693
Atrial fibrillation, n (%)	3 (7%)	8 (13%)	6 (14%)	.495
Non-sustained VT, n (%)	10 (23%)	12 (19%)	12 (28%)	.553
fQRS, n (%)	19 (44%)	34 (55%)	26 (62%)	.254
Systolic blood pressure (mm Hg)	145.7 ± 29.4	147.1 ± 27.0	148.4 ± 23.3	.905

All values were obtained from the 24-hour rhythm holter. Blood pressure was measured at the first visit to the patient.
fQRS, fragmented QRS; HR, heart rate; VES, ventricular extrasystole; VT, ventricular tachycardia.

Response to beta-blocker therapy: Following beta-blocker therapy mean and maximum heart rate decreased significantly ($P < .001$ and $P = .001$ for arginine homozygotes, $P < .001$ for glycine homozygotes, $P = .006$ and $P = .002$ for heterozygotes). Moreover, total premature ventricular contractions decreased significantly ($P = .001$ for arginine homozygotes, $P < .001$ for glycine homozygotes and $P = .002$ for heterozygotes) (Table 3).

Impact of beta-blocker therapy on NT-proBNP and LVOT gradient: Baseline NT-proBNP and LVOT gradients were similar between groups ($P = .934$ and $P = .516$, respectively). Following treatment, a decrease in NT-proBNP values was observed in all patients. This decrease was statistically significant in both the arginine homozygous and heterozygous groups ($P = .010$ and $P < .001$, respectively) but did not reach significance in the glycine homozygous group ($P = .066$). When comparing LVOT gradients after treatment, a significant gradient reduction was observed in all groups ($P < .001$) (Table 4).

Structural features: The mean maximum wall thickness was 20 ± 5 mm in Gly389 homozygote, 20 ± 5 mm in Arg389 homozygote, and 22 ± 5 mm in heterozygote individuals. There was no significant difference between the groups ($P = .230$). Left ventricular outflow tract obstruction was also similar between the groups ($P = .827$). Ventricular strain analyses demonstrated that GLS mildly decreased in the vast majority of the patients and there was no significant difference between the groups ($P = .241$) (Table 5).

Ser49Gly Polymorphism

Patients were divided into 2 groups according to Ser49Gly gene polymorphism; there were 106 patients with Ser49

Table 3. Impact of Beta-Blocker Therapy on Rhythm and Heart Rate

	Arginine389 Homozygotes	Glycine389 Homozygotes	Arg389Gly Heterozygotes
Pre-T mean HR	73.3 ± 11.0	76.4 ± 11.0	72.2 ± 11.1
Post-T mean HR	66.9 ± 8.7	67.0 ± 8.5	66.3 ± 6.9
P	<.001	<.001	.006
Pre-T maximum HR	117.9 ± 18.3	119.0 ± 17.2	113.7 ± 15.4
Post-T maximum HR	106.8 ± 14.7	107.2 ± 14.4	104.4 ± 12.6
P	.001	<.001	.002
Pre-T VES count	120 (0-2599)	126 (0-4573)	132 (0-3526)
Post-T VES count	0 (0-153)	0 (0-153)	75 (0-181)
P	.001	<.001	.002
Follow-up time	25 ± 10	27 ± 9	24 ± 8

The *P*-value for the "Follow-up time" is .304.
HR, heart rate; Post-T, post-treatment; Pre-T, pre-treatment; VES, ventricular extrasystole.

Table 6. Rate and Rhythm in Ser49Gly Polymorphism

	Ser49 Homozygotes (n = 106; 72%)	Gly Carriers (n = 41; 28%)	*P*
Pre-treatment			
Mean HR	75.2 ± 10.8	71.9 ± 11.8	.105
Maximum HR	118.9 ± 17.2	117.7 ± 16.0	.527
VES count	132 (0-4573)	56 (0-452)	.011
Atrial fibrillation, n (%)	13 (9%)	25 (17%)	.209
Non-sustained VT, n (%)	63 (26%)	20 (14%)	.116
fQRS, n (%)	86 (59%)	53 (39%)	.026
Systolic Blood pressure (mm Hg)	148±27	143±26	.581

All values were obtained from the 24-hour rhythm holter. Blood pressure was measured at the first visit to the patient.
fQRS, fragmented QRS; HR, heart rate; VES, ventricular extrasystole; VT, ventricular tachycardia.

homozygote (group 1). There were only 2 patients with Gly49 homozygote and hence rest of the patients were included in group 2 (Gly49 carriers).

Basal heart rate, rhythm and blood pressure: The mean and maximum heart rates were similar in patients with homozygote Ser49 gene and Gly carriers (*P* = .105 and *P* = .527, respectively). The incidence of atrial fibrillation and non-sustained VT were also similar between groups. Ser49 homozygotes had significantly more VES count compared to Gly carriers (*P* = .011) (Table 6). Systolic blood pressure at the first visit was comparable between the groups (148 mm Hg vs. 143 mm Hg, *P* = .581).

Response to beta-blocker therapy: Mean and maximum heart rate decreased significantly in both Ser49 homozygote and Gly carrier patients (*P* < .001 and *P* < .001 for serine homozygotes and *P* = .054 and *P* = .012 for glycine carriers, respectively) following beta-blocker therapy. However, the count of daily premature ventricular contractions decreased significantly only in Ser49 patients (*P* < .001) but not in Gly carriers (*P* = .297) (Table 7).

Impact of beta-blocker therapy on NT-proBNP and LVOT gradient: There was no significant difference in baseline NT-proBNP levels and LVOT gradients among the groups (*P* = .947 and *P* = .191, respectively). Following treatment, a

Table 4. Impact of Beta-Blocker Therapy on NT-proBNP and LVOT Gradient

	Arg389 Homozygotes	Gly389 Homozygotes	Arg389Gly Heterozygotes
Pre-T NT-proBNP	594 (5-6760)	409 (6-4551)	623 (5-4973)
Post-T NT-proBNP	146 (10-4926)	176 (10-2911)	144 (10-3917)
P	.010	.066	<.001
Pre-T LVOT gradient	38 (10-151)	39 (9-103)	39 (9-102)
Post-T LVOT gradient	14 (2-127)	15 (2-79)	15 (0-78)
P	<.001	<.001	<.001
Follow-up time	25 ± 10	27 ± 9	24 ± 8

The *P*-value for the "Follow-up time" is .304.
HR, heart rate; LVOT, left ventricular outflow tract; NT-proBNP, N-terminus pro-B-type natriuretic peptide; Post-T, post-treatment; Pre-T, pre-treatment; VES, ventricular extrasystole.

Table 5. Comparison of Structural Features Among Study Population

	Arg389 Homozygotes	Gly389 Homozygotes	Arg389Gly Heterozygotes	*P*
Maximum WT (mm)	20 ± 5	20 ± 5	22 ± 5	.230
LVEF (%)	61.4 ± 5	60.4 ± 6	59.2 ± 10	.399
GLS (%)	-15.7 ± 4	-16.1 ± 5	-14.5 ± 5	.241
LAVI (mL/m^2)	35.1 ± 13	34.0 ± 13	37.3 ± 14	.452
SAM, n (%)	13 (30%)	17 (27%)	10 (24%)	.796
LVOT obstruction, n (%)	28 (19%)	34 (23%)	34 (24%)	.827
LVOT gradient (mm Hg)	38 (10-151)	39 (9-103)	39 (9-102)	.516

GLS, global longitudinal strain; LAVI, left atrium volume index; LVEF, left ventricular ejection fraction;LVOT, left ventricular outflow tract; SAM, systolic anterior motion; WT, wall thickness.

Table 7. Impact of Beta-Blocker Therapy on Rhythm and Rate

	Serine Homozygotes	Glycine Carriers
Pre-T mean HR	75.2 ± 10.8	71.9 ± 11.8
Post-T mean HR	66.7 ± 8.1	67.2 ± 8.2
P	<.001	.054
Pre-T maximum HR	118.9 ± 17.2	112.7 ± 16.0
Post-T maximum HR	106.9 ± 13.4	104.7 ± 15.4
P	<.001	,012
Pre-T VES count	132 (0-4573)	56 (0-452)
Post-T VES count	0 (0-181)	25 (0-153)
P	<.001	.297
Follow-up time	26 ± 9	24 ± 10

The *P*-value for the "Follow-up time" is .328.
HR, heart rate; Post-T, post-treatment; Pre-T, pre-treatment; VES, ventricular extrasystole.

decrease in NT-proBNP values was observed in all patients. This decrease was statistically significant in serine homozygotes ($P < .001$). After treatment, significant reductions in LVOT gradients were observed in all groups ($P < .001$) (Table 8).

Structural features: The mean maximum wall thickness was comparable between the groups (20 ± 4 mm vs. 21 ± 5 mm, $P = .138$). Left ventricular outflow tract obstruction was detected in 24% of Ser49 homozygotes and 17% of Gly carriers ($P = .267$). Ventricular strain analyses demonstrated that GLS decreased mildly in both groups and there was no significant difference between the groups (–15.6% vs. –15.4%, $P = .833$) (Table 9).

Table 8. Impact of Beta-Blocker Therapy on NT-proBNP and LVOT Gradient

	Ser49 Homozygotes	Gly49 Carriers
Pre-T NT-proBNP	539 (5-6760)	538 (4-4973)
Post-T NT-proBNP	156 (10-4956)	158 (10-3917)
P	<.001	.075
Pre-T LVOT gradient	38 (10-151)	35 (9-74)
Post-T LVOT gradient	14 (0-127)	11 (2-50)
	< 0.001	< 0.001
Follow-up time	26 ± 9	24 ± 10

The *P*-value for the "Follow-up time" is .328.
LVOT, left ventricular outflow tract; NT-proBNP, N-terminus pro-B-type natriuretic peptide; Post-T, post-treatment; Pre-T, pre-treatment; VES, ventricular extrasystole.

Table 9. Comparison of Structural Features Among Study Population

	Ser49 Homozygotes	Gly Carriers	*P*
Maximum WT (mm)	21 ± 5	20 ± 4	.138
LVEF (%)	61 ± 6	58 ± 10	.019
GLS (%)	–15.6 ± 5	–15.4 ± 4	.833
LAVI (mean, mL/m^2)	35.1 ± 14	35.6 ± 12	.842
SAM, n (%)	41 (28%)	35 (24%)	.630
LVOT obstruction, n (%)	35 (24%)	25 (17%)	.267
LVOT gradient (mm Hg)	38 (10-151)	35 (9-74)	.191

GLS, global longitudinal strain; LAVI, left atrium volume index; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; SAM, systolic anterior motion; WT, wall thickness.

DISCUSSION

In this study, we searched for the potential effect of 2 common polymorphisms in adrenoceptor beta-1 gene polymorphism on the heart rate and rhythm and response to beta-blocker therapy in patients with hypertrophic cardiomyopathy. Our findings show that the Arg389Gly polymorphism does not have significant effect on the baseline heart rate and response to beta blocker therapy. However, Ser49Gly polymorphism appears to have significant effect on the VES count and suppressibility with beta blockers. In addition, following beta-blocker therapy, natriuretic peptide levels and left ventricular outflow obstruction decreased significantly.

The adrenergic system plays a central role during the course of HCM via increasing heart rate and myocardial contractility which further deteriorates LV diastolic functions and hence beta-blocker therapy has become the cornerstone of medical treatment of symptomatic HCM patients. Our results indicated that beta-blocker therapy reduces mean and maximum heart rate in hypertrophic cardiomyopathy patients regardless of ADRB-1 gene polymorphisms. Moreover, apart from Gly49 carrier subgroup, the total number of daily VES decreases significantly underlying the efficacy of beta-blocker therapy in HCM patients. Previous studies demonstrated that polymorphisms of the genes encoding beta-1 adrenergic receptors, particularly those resulting in amino acid substitution at the 49th and 389th positions, may have effects on the response to the adrenergic system and response to beta-blocker therapy.[9-12] However, the results of the studies are inconsistent. In vitro studies by Rathz et al[8] and Levin et al,[9] chronic exposure to a beta-receptor agonist resulted in the downregulation of beta-receptors in Gly49 carriers which did not observe in Ser49 homozygous.[8,9] They concluded that Gly49 carrier heart failure patients may have better outcomes. In our study, the mean heart rate prior to beta-blocker therapy was higher in Ser49 homozygous and following beta-blocker therapy, the mean heart rate decreased significantly in Ser49 homozygote and Ser49Gly heterozygote patients. This finding indicates that Ser49 homozygote patients are more susceptible to adrenergic stimulation and beta-blocker therapy is more efficacious in these patient groups which is concordant with Rathz et al[8] findings. Lanfear et al[13] have studied the effect of beta-blocker in patients with heart failure and concluded that beta-blocker therapy is 5 times more effective in Ser49 homozygous which is in line with our findings. Talameh et al[14] also studied a similar patient subset and concluded that the survival benefit of beta-blocker therapy in heart failure patients is detected in Ser49 homozygous, not heterozygous. In our study, there was no significant impact of Arg389Gly polymorphism on heart rate and response to beta-blocker therapy. Although the literature includes

several studies which have reported that Arg389Gly polymorphism has a significant effect on left ventricular remodeling and response to beta-blocker therapy, there are also several studies reporting contradicting data. In light of these conflicting results, the effect of Arg389Gly polymorphism needs to be clarified.

The principal goal of beta-blocker therapy is to reduce the symptoms particularly those associated with increased myocardial contractility. In this study, we search for the impact of beta-blocker therapy on the quantitative parameters including natriuretic peptides and outflow gradient. Our results demonstrated that following beta-blocker therapy natriuretic peptide levels decreased in all HCM patients particularly in patients with Ser49 homozygotes. Concordant with natriuretic peptide levels, left ventricular outflow obstruction was also decreased in all patients. Recently Dybro et al. investigated the impact of beta-blocker therapy on haemodynamic and structural variables among obstructive HCM patients and demonstrated lower LVOT gradient following beta-blocker therapy and increased LV end-diastolic diameter.[15] Our results are in line with aforementioned study. Geske et al[16] search for the potential utility of natriuretic peptides in HCM patients and concluded that septal reduction therapy which resolves LVOT obstruction significantly is associated with decreased natriuretic peptides. Hamada et al[17] demonstrated that chronic use of cibenzoline, a class 1A antiarrhytmic drug with negative inotropic properties, resulted in lower natriuretic peptide levels among HCM patients. Increased left ventricular end-diastolic volume due to prolonged diastole, decreased myocardial contractility and LVOT obstruction might be associated with decrease in natriuretic peptide levels. In this regard, further studies are needed to clarify our findings.

Study Limitations

Although this is a prospective study, there are several limitations. The major limitation of our study is the under-representation of high-risk HCM patients. The reason for this was patients admitted with palpitations/syncope were hospitalized in the intensive unit to detect VAs and ICD implantation was performed without cardiac MRI confirmation. The second limitation was being unable to report clinical outcomes. Although we recorded clinical outcomes, due to the lower number of cardiovascular events, the comparison would likely be misleading and hence we did not report the outcomes. Additionally, the limited number of participants in our study is another notable limitation, which may impact the generalizability of our findings.

CONCLUSION

In conclusion, we have demonstrated that polymorphism in the adrenoceptor beta-1 gene, particularly Ser49Gly polymorphism, is associated with structural and clinical features among patients with hypertrophic cardiomyopathy. Moreover, Ser49Gly polymorphism has a significant impact on response to beta-blocker therapy. Further studies with higher populations and longer follow-ups are needed to determine the role of adrenoceptor beta-1 gene polymorphism for the risk assessment and treatment strategy in patients with hypertrophic cardiomyopathy.

Ethics Committee Approval: The ethics committee approval for the study was provided by the İstanbul University-Cerrahpaşa Ethics Committee (date: August 10, 2018; number: 30330229-6040102-42266).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

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