Key genetic variants in the renin-angiotensin system and left ventricular mass in a cohort of Polish patients with heart failure

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ABSTRACT

Background: Heart failure (HF) is a complex disease that is under the control of different physiological systems. Left ventricular mass (LVM) is a strong predictor of HF. The renin-angiotensin system (RAS) may contribute to the pathogenesis of HF and LVM.

Aims: The aim of this study is to examine the association between RAS genetic variants and HF and LVM in the cohort of Polish patients with HF.

Methods: The study included 401 patients with HF. Two-dimensional M-mode echocardiography was used to assess LVM. Genomic DNA was extracted from blood, and genotyping of the angiotensin-converting enzyme (*ACE*) (rs4646994), angiotensinogen (*AGT*) (rs5051), and angiotensin II receptor type 1 (*AGTR1*) (rs5186) polymorphisms was carried out using polymerase chain reaction (PCR).

Results: A significant association was found between HF and the genotypes of G(–6)A *AGT*, and the homozygotes AA of *AGT* were significantly less common in the HF vs control group. The results of this study did not confirm the relationship between *AGT*, *ACE* and *AT1R* genetic variants with LVM in Polish patients with HF.

Conclusions: Our results suggested that *AGT* polymorphism may play a protective role in the development of HF.

Key words: genes, heart failure, left ventricular mass, renin-angiotensin system

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INTRODUCTION

Heart failure (HF) is a growing global health problem that is also responsible for high mortality. The most common causes of HF are ischemic heart disease (IHD), hypertension (HT), valvular heart disease (VD) or cardiomyopathy [1]. However, it is known that the etiology of HF is complex and researchers are still looking for factors that influence the development and progression of HF.

It is already known that the renin-angiotensin system (RAS) plays an important role in the pathophysiology of left ventricular (LV) dysfunction, left ventricular hypertrophy (LVH), regulation of arterial pressure, cardiovascular diseases, and thus, HF [2]. Angiotensinogen (*AGT*), angiotensin-converting enzyme (*ACE*) and angiotensin II receptor type 1 (*AGTR1*) are key components of RAS. So far, researchers have shown that *AGT* polymorphisms are mainly associated with the development of HT or IH [3, 4], while the correlations with HF remain inconsistent [5, 6]. However, some studies indicate a correlation between *AGT* gene polymorphism and increased left ventricular mass (LVM) [7, 8], and LVH is a strong predictor of HF [9].

The insertion/deletion polymorphism (I/D) of the *ACE* gene is the most extensively studied and has been shown to be correlated with HT, IHD and other cardiovascular intermediate phenotypes [10–15]. Moreover, *ACE* has been known to have a crucial role in the development of cardiac

WHAT'S NEW?

Heart failure (HF) is a major cause of morbidity and mortality in the world. The renin-angiotensin system (RAS) plays an important role in the pathophysiology of HF development and left ventricular dysfunction. Left ventricular mass (LVM) is a major contributor to the development of heart failure. The search for genetic variants that could act as prognostic markers that could be used to predict poor outcomes and assist in selecting appropriate therapy is still ongoing. To determine the relationship between the key RAS genetic variants: G(–6)A angiotensinogen (*AGT*), insertion/deletion polymorphism of angiotensin-converting enzyme (I/D *ACE*) or A1166C angiotensin II receptor type 1 (*AGTR1*), and HF or LVM, we studied 401 Polish patients with HF. Our results suggested that *AGT* polymorphism may play a protective role in the development of HF.

remodeling by either angiotensin II or aldosterone [16]. There are some reports that suggest that this polymorphism is associated with increased LVM in normotensive and hypertensive patients or in patients with cardiomyopathy [17, 18], although there are studies that do not support this correlation [19, 20]. While the genetic determinants of LVM in patients with HF have not been so extensively studied, the role of the I/D *ACE* polymorphism in shaping LVM is not fully understood. There is no direct reporting targeting of genetic predisposition to increase LVM in patients with HF, and the role of I/D *ACE* polymorphism in LVM modulation may be significant, and thus, for HF may be of pivotal importance.

The effect of *AGTR1* on the regulation of LVM was also demonstrated, as it was found to influence the regulation of blood volume and stimulate the growth and proliferation of heart cells, which causes the development of HF [21]. However, the results of available studies remain controversial and other studies were not able to detect any influence of RAS gene polymorphisms on LVM [22, 23]. Although the potential role of the RAS system in structure and heart disorders is relatively well understood, these molecular mechanisms involved in LVM in patients with HF continue to be studied. Especially, RAS genetic polymorphisms involved in HF pathophysiology are of particular interest as the plausible candidates may play a role in modifying LVM.

Therefore, the aim of our study was to analyze the association between the G(–6)A *AGT* (rs5051), I/D *ACE* (rs4646994) and A1166C *AGTR1* (rs5186) genetic variants and both HF and the LVM in a cohort of Polish patients with HF.

METHODS

Patients

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local bioethics committee at the Pomeranian Medical University (PMU) in Szczecin, Poland. Written informed consent was obtained from study participants.

This was a case-control study of patients with a diagnosis of HF from Department of Cardiac Surgery and Cardiology Department of PMU. A total of 401 patients (293 men, 108 women) included in the study had symptomatic HF, defined as New York Heart Association (NYHA) functional class I–IV. The study group with HF included patients with IHD (n = 245; 192 men, 53 women), patients with VD (n = 68; 37 men, 31 women), and patients with combined disease, IHD and VD (n = 88; 64 men, 24 women). Among these HF patients were 195 patients with reduced ejection fraction <50% (HF with reduced ejection fraction [HfrEF] subgroup). Doppler echocardiography was used to examine LV dysfunction.

Demographic data and medical history of patients were collected from their medical chart records. The control group was consisted of 120 volunteers (43 men, 77 women) without history of cardiac disease.

Echocardiography

Transthoracic echocardiography was performed using an Acuson Sequoia 512 unit (Siemens, Munich, Germany) equipped with a 2–4 MHz imaging transducer, according to the recommendations of the American Society of Echocardiography (ASE). Measurements of LV end-diastolic diameter (LVEDD), LV septal wall thickness diameter (IVTd) and posterior wall thickness diameter (PWTd) were obtained in the M-mode parasternal long-axis view. An average of values after three image acquisitions was calculated. In cases with suboptimal M-mode acquisition, measurements in two-dimensional views were obtained instead. LVM was calculated with the ASE-recommended formula [24]: LVM (g) = 0.8 × {1.04 [(LVEDD + PWTd + IVTd)3 – (LVEDD)3]} + 0.6 g. Body surface area was calculated using the Mosteller formula {square root [height (cm) × weight (kg)]/3600} and LVM was indexed to the body surface area. LVH was defined as LV mass index (LVMI) >115 g/m^2 in men and >95 g/m^2 in women [24].

Genotyping

Genomic DNA was isolated from whole blood collected into ethylenediaminetetraacetic acid tubes using the QIAamp Blood DNA Mini Kit (QIAGEN, Hilden, Germany).

For the analysis, a polymerase chain reaction and polymerase chain reaction/restriction fragments length polymorphism (PCR/RFLP) method were applied. Genotyping of the G(–6)A *AGT* (rs5051), I/D *ACE* (rs4646994) and

A1166C *AGTR1* (rs5186) polymorphisms were carried out as previously described [25].

Statistical analysis

The distributions of all quantitative variables, except age, were significantly different from normal distribution (P <0.05, Shapiro-Wilk's test). Therefore, quantitative variables were presented as the median with lower quartile and upper quartile, and analyzed using the non-parametric Kruskal-Wallis or the Mann-Whitney U test. Qualitative variables were presented as number with corresponding percentage and compared between groups with the chi-square or the Fisher exact test. Concordance of genotype distribution with Hardy-Weinberg equilibrium was performed with the exact test. Strength of association of qualitative variables with genotypes and alleles was described as odds ratio (OR) with 95% confidence interval (95% CI). Multivariable logistic regression analysis adjusted for age and sex was performed to verify whether the associations of genetic polymorphisms with HF are independent of these demographic factors. P <0.05 was considered statistically significant without correction for multiple tests. Bonferroni-corrected P-value thresholds were calculated as follows: for the study of associations between HF and each of the 3 polymorphisms in 4 models of inheritance (dominant, recessive or additive mode for minor allele as well as comparison of wild-type homozygotes with mutated ones), $3 \times 4 = 12$ tests were performed, so the corrected P-value threshold was 0.05/12 = 0.0042; for the study of associations between LVMI and each of the 3 polymorphisms in 4 aforementioned models of inheritance in the whole group of HF patients and in the subgroups with arterial hypertension or with HFrEF, $3 \times 4 \times 3 = 36$ tests were performed, so the corrected P-value threshold was 0.05/36 = 0.0014. Calculations were performed with Statistica 13 software (Statistica, Dell Inc. [2016], version 13, software.dell.com).

RESULTS

The baseline characteristics of the HF subjects is shown in Table 1. The BMI and age proved to be significantly higher in the HF group, when compared to controls. Similarly, smoking, diabetes, and HT were more common among HF patients than controls. Significant differences in all echocardiographic parameters were noted between HF patients and controls (higher IVT, PWT, LVM, LVMI, LVEDD and lower ejection fraction [EF] values in the HF group) (Table 1).

The G(–6)A *AGT*, I/D *ACE* and A1166C *AGT1R* gene polymorphism genotypes were found to be in Hardy-Weinberg equilibrium both in the HF and control group (P >0.1). We observed a significant association between HF and genotypes of G(–6)A *AGT* (Table 2). Analyses revealed that homozygotes AA of *AGT* are significantly less common in the HF group than in the control group (P = 0.014). The negative association between AA *AGT* genotype and HF was even stronger in multivariable logistic regression model adjusted for age and sex (OR, 0.427; 95% CI, 0.245–0.742; P = 0.0025), reaching the Bonferroni-corrected P-value threshold (<0.0042). No association was found between I/D *ACE* or A1166C *AGT1R* gene polymorphism and HF, both in univariable and multivariable analyses (P >0.3).

The results of association of the G(–6)A *AGT*, I/D *ACE* and A1166C *AGT1R* polymorphisms with LVMI in HF patients are summarized in Table 3. We did not detect any significant correlations. The results of these tests on the effects of G(–6)A *AGT*, I/D *ACE* and A1166C *AGT1R* polymorphisms with LVH defined as LVMI >115 g/m^2 in men and >95 g/m^2 in women are presented in Table 4. We did not find any significant correlations.

We also found no relationship between the studied polymorphisms and LVMI in the subgroup of patients with HF and arterial hypertension (n = 309; P >0.1; data not shown).

Subsequently, we conducted an analysis of the effect of G(–6)A *AGT*, I/D *ACE* and A1166C *AGT1R* genotypes on LVH in a subgroup of HF patients with HFrEF <50% (Table 5).

Table 1. Clinical and echocardiographic characteristics of patients with HF and control group

Characteristics	HF cases (n = 401)	Control (n = 120)	P-value[a]
Age, years	66.0 (61.0–71.0)	56.0 (49.0–63.0)	<0.0001
BMI, kg/m^2	29.0 (25.8–31.7)	27.3 (24.8–29.4)	<0.0001
Males	293 (73)	77 (64)	0.077
Smoking	126 (31)	24 (20)	0.021
Diabetes mellitus	258 (64)	9 (7)	<0.0001
Hypertension	337 (84)	24 (20)	<0.0001
Echocardiographic parameters			
IVT, cm	1.25 (1.10–1.40)	0.97 (0.95–1.00)	<0.0001
PWT, cm	1.10 (1.00–1.25)	1.05 (1.00–1.10)	<0.0001
LVEDD, cm	5.00 (4.61–5.50)	4.75 (4.31–5.05)	<0.0001
EF, %	50.0 (40.0–55.0)	64.0 (62.0–67.2)	<0.0001
LVM, g	241.8 (195.9–293.8)	171.5 (147.9–190.3)	<0.0001
LVMI, g/m^2	125.7 (99.3–149.5)	88.8 (76.0–102.5)	<0.0001

Quantitative variables are presented as median (IQR) and qualitative data are presented as a number with corresponding percentage.

[a]The Fisher exact test for qualitative variables and the Mann-Whitney U test for quantitative variables.

Abbreviations: BMI, body mass index; EF, ejection fraction; HF, heart failure; IVT, left ventricular septal wall thickness; LVEDD, left ventricular end-diastolic diameter; LVM, left ventricular mass; LVMI, left ventricular mass index; PWT, posterior wall thickness

Table 2. Genotype frequencies for G(–6)A *AGT*, I/D *ACE*, A1166C *AGT1R* in patients with HF and control group

Polymorphism	HF group (n = 401)		Control group (n = 120)		*P*-value[a]	Compared genotypes or alleles	OR (95% CI)	*P*-value[b]
AGT genotype								
GG	108	26.9%	31	25.8%	0.042	AA + GA vs GG	0.945 (0.594–1.504)	0.811
GA	215	53.6%	53	44.2%		AA vs GA + GG	0.564 (0.355–0.895)	0.014[c]
AA	78	19.6%	36	30.0%		AA vs GG	0.622 (0.355–1.091)	0.096
AGT allele								
G	431	53.7%	115	47.9%	—	A vs G	0.792 (0.593–1.057)	0.113
A	371	46.3%	125	52.1%	—			
ACE genotype								
II	92	22.9%	27	22.5%	0.99	DD + ID vs II	0.975 (0.599–1.588)	0.919
ID	207	51.6%	62	51.7%		DD vs ID + II	0.979 (0.614–1.562)	0.930
DD	77	25.5%	31	25.8%		DD vs II	0.966 (0.536–1.738)	0.907
ACE allele								
I	391	48.8%	116	48.3%	—	D vs I	0.983 (0.737–1.312)	0.909
D	411	51.2%	124	51.7%	—			
AGTR1 genotype								
AA	219	54.6%	61	50.8%	0.73	CC + AC vs AA	0.859 (0.571–1.293)	0.466
AC	154	38.4%	49	40.8%		CC vs AC + AA	0.826 (0.389–1.753)	0.618
CC	28	7.0%	10	8.4%		CC vs AA	0.780 (0.359–1.694)	0.529
AGTR1 allele								
A	592	73.8%	171	71.3%	—	C vs A	0.879 (0.638–1.212)	0.431
C	210	26.2%	69	28.8%	—			

[a]The Chi-square test for difference in frequencies of 3 genotypes. [b]The Chi-square test for difference in frequencies of 2 genotypes, genotype groups or alleles. [c]OR, 0.427; 95%CI, 0.245–0.742; *P* = 0.0025 in multivariable logistic regression model adjusted for age and sex.

Abbreviations: ACE, angiotensin-converting enzyme; AGT, angiotensinogen; AGTR1, angiotensin II receptor type 1; CI, confidence interval; HF, heart failure; I/D, insertion/deletion; OR, odds ratio

Table 3. Association of G(–6)A *AGT*, I/D *ACE*, A1166C *AGTR1* genotypes and LVMI in HF patients (n = 401)

Polymorphism	LVMI, g/m²	*P*-value[a]	Compared genotypes	*P*-value[b]
AGT genotype				
GG	126.2 (94.6–153.6)		AA + GA vs GG	0.953
GA	121.3 (98.3–146.1)	0.268	AA vs GA + GG	0.126
AA	132.8 (103.2–152.9)		AA vs GG	0.315
ACE genotype				
II	126.1 (99.3–150.0)		DD + ID vs II	0.689
ID	126.1 (101.5–152.8)	0.290	DD vs ID + II	0.116
DD	118.8 (96.2–141.0)		DD vs II	0.233
AGTR1 genotype				
AA	121.4 (100.7–145.4)		CC + AC vs AA	0.284
AC	132.5 (99.8–155.6)	0.241	CC vs AC + AA	0.357
CC	116.9 (88.0–142.8)		CC vs AA	0.516

LVMI is presented as median (IQR).

[a]The Kruskal-Wallis test. [b]The Mann-Whitney U test.

Abbreviations: see Table 1 and Table 2

The presence of the DD *ACE* genotype was significantly associated with a lower prevalence of LVH in patients with HFrEF (OR, 0.450 [95%CI 0.226–0.895]; *P* = 0.021). However, this association did not reach Bonferroni-corrected *P*-value threshold (<0.0014).

DISCUSSION

This study evaluated the role of the G(–6)A *AGT*, I/D *ACE* and A1166C *AGTR1* polymorphisms with HF and LVM in patients with HF. Although the association between the RAS polymorphisms and cardiovascular disease has been demonstrated in many previous studies, this relationship is still controversial. The importance of RAS polymorphisms in relation to HF has not been fully explained and is still widely discussed, and reports on these issues are contradictory. To our knowledge, this is the first cohort study that examined the association of the key RAS gene polymorphisms and HF and LVM in Polish patients. The present study demonstrated a correlation between HF and the AA genotype of the *AGT* gene.

Excessive circulating and tissue angiotensin II and aldosterone levels have been shown to lead to a profibrotic, proinflammatory, and prohypertrophic milieu that causes remodeling and dysfunction in cardiovascular and renal tissues [26]. Therefore, molecular variants of RAS are considered to be important for LVM, and thus, HF. To date, the relationship of M235T *AGT* polymorphism and HF was the most studied. It has been demonstrated that the con-

Table 4. Association of G(–6)A *AGT*, I/D *ACE*, A1166C *AGTR1* genotypes and LVH in HF patient group (n = 401)

Polymorphism	Patients with LVH (n = 262)		Patients without LVH (n = 139)		*P*-value[a]	Compared genotypes or alleles	OR (95% CI)	*P*-value[b]
AGT genotype								
GG	71	27.1%	37	26.6%	0.23	AA + GA vs GG	0.976 (0.613–1.553)	0.918
GA	134	51.6 %	81	58.3%		AA vs GA + GG	1.562 (0.902–2.706)	0.109
AA	57	21.8 %	21	15.1%		AA vs GG	1.414 (0.747–2.680)	0.287
AGT allele								
G	276	52.7%	155	55.8%	—	A vs G	1.132 (0.845–1.517)	0.405
A	248	47.3%	123	44.2%	—			
ACE genotype								
II	62	23.7%	30	21.6%	0.28	DD + ID vs II	0.888 (0.542–1.456)	0.637
ID	140	53.5%	67	48.2%		DD vs ID + II	0.686 (0.432–1.090)	0.109
DD	60	22.9%	42	30.2%		DD vs II	0.828 (0.619–1.109)	0.205
ACE allele								
I	264	50.4%	127	45.7%	—	D vs I	0.828 (0.619–1.109)	0.205
D	260	49.6%	151	54.3%	—			
AGTR1 genotype								
AA	139	53.1%	80	57.6%	0.49	CC + AC vs AA	1.200 (0.793–1.817)	0.389
AC	106	40.5%	48	34.5%		CC vs AC + AA	0.807 (0.367–1.775)	0.594
CC	17	6.5%	11	7.9%		CC vs AA	0.890 (0.397–1.993)	0.776
AGTR1 allele								
A	384	73.2%	70	25.2%	—	C vs A	1.083 (0.777–1.511)	0.637
C	140	26.7%	208	74.82%	—			

[a]The Chi-square test for difference in frequencies of three genotypes. [b]The Chi-square test for difference in frequencies of two genotypes, genotype groups or alleles.
Abbreviations: see Table 1 and Table 2

Table 5. Association of G(–6)A *AGT*, I/D *ACE*, A1166C *AGTR1* genotypes and LVH in HF patients with reduced ejection fraction (n = 195)

Polymorphism	HFrEF patients with LVH (n = 138)		HFrEF patients without LVH (n = 57)		*P*-value[a]	Compared genotypes or alleles	OR (95% CI)	*P*-value[b]
AGT genotype								
GG	36	26.1%	13	22.8%	0.889	AA + GA vs GG	0.837 (0.405–1.730)	0.631
GA	77	55.8%	33	57.9%		AA vs GA + GG	0.925 (0.421–2.034)	0.847
AA	25	18.1%	11	19.3%		AA vs GG	0.821 (0.317–2.125)	0.684
AGT allele								
G	149	54.0%	59	51.8%	—	A vs G	0.914 (0.591–1.416)	0.688
A	127	46.0%	55	48.3%	—			
ACE genotype								
II	38	27.5%	11	19.3%	0.063	DD + ID vs II	0.629 (0.295–1.341)	0.228
ID	73	52.9%	26	45.6%		DD vs ID + II	0.450 (0.226–0.895)	0.021
DD	27	19.6%	20	35.1%		DD vs II	0.391 (0.161–0.948)	0.035
ACE allele								
I	149	54.0%	48	42.1%	—	D vs I	0.620 (0.399–0.963)	0.033
D	127	46.0%	66	57.9%	—			
AGTR1 genotype								
AA	72	52.2%	33	57.9%	0.632	CC + AC vs AA	1.260 (0.676–2.350)	0.466
AC	54	39.1%	21	36.8%		CC vs AC + AA	1.714 (0.465–6.320)	0.413
CC	12	8.7%	3	5.3%		CC vs AA	1.833 (0.486–9.360)	0.366
AGTR1 allele								
A	198	71.7%	87	76.3%	—	C vs A	1.269 (0.766–2.103)	0.354
C	78	28.3%	27	23.7%	—			

[a]The Chi-square test for difference in frequencies of three genotypes. [b]The Chi-square test for difference in frequencies of two genotypes, genotype groups or alleles.
Abbreviations: HFrEF, HF patients with reduced ejection fraction; LVH, left ventricular hypertrophy; other, see Table 1 and Table 2

centration of *AGT* in blood increases with the number of T235 alleles [27]. Some studies demonstrate that this single nucleotide polymorphism (SNP) of *AGT* may be associated with HF in different populations [27, 28], whereas some studies did not find associations between M235T *AGT* and HF [7, 29]. In our study, we examined the association between the G(–6)A *AGT* polymorphism with HF, and this polymorphism remains in very tight linkage disequilibrium with T235 *AGT* and marks the original form of the gene. The functionality of (–6G) *AGT* variants was demonstrated by their influence on the basal transcription rate [30]. In this study, we found association between G(–6)A of *AGT* and HF in our population, the analysis revealed the protective role of the homozygotes AA for HF. Additionally, we noted the

lack of association of the I/D *ACE* and A1166C *AGTR1* polymorphisms. The obtained result of the correlation of (–6) *AGT* polymorphism with HF may result from the different concentration of *AGT*. Given the important role of *AGT* in regulating RAS, it is likely that the *AGT* polymorphism may modulate the risk of developing HF in the Polish population. However, these findings still need to be clarified.

The association between RAS polymorphisms and LVH has been demonstrated in numerous published studies [31, 32]. However, the relationship between these polymorphisms and LVM and HF is still not fully understood, and better understanding of the complexity of RAS should help modulate this system and consequently improve quality of life. As it is known, in the course of HF during pressure overload, there is myocardial remodeling, which leads to myocardial hypertrophy, as the result of adaptation to mechanical workload demands. However, under pathological conditions of the onset of HF, myocardial remodeling reactions often become maladjusted, leading to myocardial decompensation. This phenomenon is associated with increased wall stress, insufficient or inappropriate cardiomyocyte hyperplasia, apoptosis or increased fibrosis [26].

In our study, we did not demonstrate any relationship between the RAS genes studied and LVM.

This relatively weak influence of genetic factors on LVM in our patients with HF may be due to a strong influence of risk factors of HF. In the Polish population, traditional risk factors for cardiovascular diseases (e.g., obesity, HT, diabetes mellitus, smoking, etc.) are still widespread, and as presented by Favé at al. [33], local environment directly influences disease-risk phenotypes and genetic variation, including fewer common variants, and can also modulate individual responses to environmental challenges. Previously, we presented a study in which we showed that *ACE*, *AT1R* and *MTHFR* gene polymorphisms do not predispose to a greater LVM in Polish patients with myocardial infarction [34].

Furthermore, it should be noted that the patients in our program were treated for HF (mainly with ACE inhibitors, angiotensin receptor antagonists, calcium inhibitors, etc.), especially with drugs from the group of which RAS inhibitors may modulate LVM, which may have affected our results. It has been proven in numerous studies that the inhibition of the RAS as a result of the use of drugs from the group of ACE inhibitors influences the course of disease processes [35, 36].

Moreover, another study demonstrated a genetic influence of antihypertensive treatment and the effect of RAS blockers on the regression of LVH [37]. It is known that ACE inhibitors are among the basic drugs used in the treatment of patients with HF and asymptomatic left ventricular dysfunction, as they prevent disease progression, have protective effects of LVH, and reduce mortality and the frequency of hospitalization [35].

Although RAS is an important contributor to LVM modulation, the contribution and serious consequences of HT should be considered. In our study, we did not observe the influence of the studied genes on LVM in patients with HF who also had HT. We believe this finding can only confirm that proper treatment of HT can protect patients against myocardial hypertrophy. Many studies have shown that appropriate treatment of the effects of HT is associated with the regression of LVH [37, 38]; especially antihypertensive treatment with ACE inhibitors in patients with the DD genotype of the *ACE* gene presenting the best response to LVH regression [39].

The limitation of this study is the relatively small study group. Moreover, the etiology of HF in the study group is diverse, which may affect the obtained results.

HF is a complex disease and the genetic components involved in its development are based on the action of many genes. Of particular note is LVH in the course of HF, which is the main factor influencing the advancement of the disease process, and the exact mechanism of which is still not fully clear. As a result, the search for genes that can act as prognostic markers that could be used to predict poor outcomes and aid in selecting the appropriate therapeutic intervention is still ongoing. Further study on this complex system is necessary to improve medical therapies for cardiovascular diseases, allowing us to more adeptly modulate this system and improve clinical outcomes.

CONCLUSIONS

Our results suggested that polymorphism G(–6)A of the *AGT* gene may play a protective role in the development of HF in Polish patients. However, further multi-center studies of ethnically diverse populations are needed to confirm this finding in the future.

Article information

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