Angiotensin-Converting Enzyme Genetic Polymorphism: Its Impact on Cardiac Remodeling

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Abstract

Background: The role of angiotensin-converting enzyme genetic polymorphisms as a predictor of echocardiographic outcomes on heart failure is yet to be established. The local profile should be identified so that the impact of those genotypes on the Brazilian population could be identified. This is the first study on exclusively non-ischemic heart failure over a follow-up longer than 5 years.

Objective: To determine the distribution of angiotensin-converting enzyme genetic polymorphism variants and their relation with echocardiographic outcome of patients with non-ischemic heart failure.

Methods: Secondary analysis of the medical records of 111 patients and identification of the angiotensin-converting enzyme genetic polymorphism variants, classified as DD (Deletion/Deletion), DI (Deletion/Insertion) or II (Insertion/Insertion).

Results: The cohort means were as follows: follow-up, 64.9 months; age, 59.5 years; male sex, 60.4%; white skin color, 51.4%; use of beta-blockers, 98.2%; and use of angiotensin-converting-enzyme inhibitors or angiotensin receptor blocker, 89.2%. The angiotensin-converting enzyme genetic polymorphism distribution was as follows: DD, 51.4%; DI, 44.1%; and II, 4.5%. No difference regarding the clinical characteristics or treatment was observed between the groups. The final left ventricular systolic diameter was the only isolated echocardiographic variable that significantly differed between the angiotensin-converting enzyme genetic polymorphisms: 59.2 ± 1.8 for DD versus 52.3 ± 1.9 for DI versus 59.2 ± 5.2 for II (p = 0.029). Considering the evolutionary behavior, all echocardiographic variables (difference between the left ventricular ejection fraction at the last and first consultation; difference between the left ventricular systolic diameter at the last and first consultation; and difference between the left ventricular diastolic diameter at the last and first consultation) differed between the genotypes (p = 0.024; p = 0.002; and p = 0.021, respectively).

Conclusion: The distribution of the angiotensin-converting enzyme genetic polymorphisms differed from that of other studies with a very small number of II. The DD genotype was independently associated with worse echocardiographic outcome, while the DI genotype, with the best echocardiographic profile (increased left ventricular ejection fraction and decreased left ventricular diameters). (Arq Bras Cardiol. 2014; 102(1):70-79)

Keywords: Heart failure; Genetic polymorphism; Angiotensin-converting enzyme.

Introduction

Heart failure (HF) is the second major cause of hospitalization in Brazil[1]. In the United States, 32 billion dollars will be spent during 2013[2] with that syndrome. In addition, those patients' quality of life is severely impaired. Despite the reduction in morbidity and mortality due to new drugs, that gain has not been uniform, and clinical outcome can be unfavorable. One of the mechanisms that can justify such differences is genetics.

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Manuscript received June 01, 2013; revised manuscript July 23, 2013; accepted July 25, 2013.

DOI: 10.5935/abc.20130229

The genetic influence, comprising all stages of the syndrome[3], has been studied in the following phases: pre-installation[4]; development[5]; and clinical phase (disease natural history[6] and therapeutic response[7]). Those results are controversial[8] and the studies have been carried out in foreign populations; thus, their impact on the Brazilian population remains unclear.

The major mechanism of that genetic influence is via modulation of the activity of the sympathetic nervous (SNS) and renin-angiotensin-aldosterone (RAAS) systems, which promote cardiac remodeling and sodium and water retention, characteristics of HF. Variations in the activity of those systems would determine different pathophysiological responses, and, thus, varied clinical outcome.

Some genetic markers, the genetic polymorphisms (GP), have been identified and associated with the molecular processes of that neuro-humoral response, such as beta-adrenergic receptors[7], angiotensin synthesis[9], nitric oxide metabolism[10], and angiotensin converting enzyme

(ACE)[4,11-19]. The later, object of this study, is the major agent of the RAAS.

Regarding RAAS, the major GP was the ACE Deletion/Insertion (DI) of 287 base pairs of the intron 16 (GPACE)[20]. The GPACE, especially the Deletion/Deletion (DD) genotype, was associated with the risk for HF[21], mortality[22], rejection to heart transplants[23], and echocardiographic variations[24]. However, that relationship has not been observed in some publications[11,19,25].

Published studies have controversial results and small sample sizes, and have been carried out in populations different from the Brazilian one, regarding geographical, epidemiological and ethnical aspects. In addition, patients with non-ischemic HF are usually underrepresented in studies on the topic, involving different pathophysiological mechanisms[26] and variable therapeutic responses[27].

Thus, the present study aimed at determining the frequency of the GPACE variants and their relation with the clinical and echocardiographic outcomes of patients with non-ischemic HF.

Methods

Study design

This is a longitudinal study of a cohort of patients. Medical data were retrospectively and prospectively collected from their medical records, beginning at the patient's arrival at the HF Clinics of a university-affiliated hospital, from December 2009 to January 2012.

Patients

This study consecutively selected 111 patients (67 men and 44 women) diagnosed with systolic non-ischemic HF, on a minimum 12-months follow-up. The major characteristics of the sample were as follows: mean age, 59.5 ± 1.3 years (range: 26 - 89 years); male prevalence (60.4%); and ethnical composition (white, 51.4%; black, 36.0%; others, 12.6%). The mean follow-up time was 64.9 ± 3.9 months.

Inclusion criteria

Patients with symptomatic non-ischemic HF, according to the Framingham criteria, and systolic ventricular dysfunction with ejection fraction ≤ 50% on two-dimensional echocardiography (Simpson's method) were considered eligible to the study.

Exclusion criteria

The presence of significant coronary arterial disease defined as coronary lesion ≥ 75% in two or more epicardial arteries or ≥ 75% in left main coronary artery[28] led to exclusion from this study.

Heart failure etiology

The HF etiologies were classified into four groups: idiopathic (36.0%); hypertensive (20.7%); alcoholic (18.9%); and others (24.3%). The diagnosis was established by the physician at the HF Clinics, according to previously described criteria[29].

Clinical, laboratory and electrocardiographic parameters

Clinical data were extracted from medical records. Skin color was defined by the attending physician and classified as white, black or others. The functional class was determined according to the New York Heart Association functional classification, at the beginning and end of follow-up.

Laboratory tests were periodically performed at the discretion of the attending physician. The most recently available exams were considered for analysis to express the patient's current clinical status.

All patients underwent electrocardiography (ECG), and were assessed regarding QRS duration, presence of left bundle-branch block (LBBB) and atrial fibrillation (AF).

Echocardiographic variables

The following parameters were assessed: left ventricular systolic diameter (LVSD); left ventricular diastolic diameter (LVDD); and left ventricular ejection fraction (LVEF). Echocardiography was performed by a medical team blinded to the patients' genotypes. Two echocardiographies were performed, one at the beginning and another at the end of follow-up, with a mean interval between exams of 65.5 ± 4.3 months (range: 12 – 232 months), so that the evolution of those parameters could also be observed.

Genotyping

The GPACE variants were analyzed from blood samples collected. After storage under a temperature of 5-15°C, the samples were processed and the DNA extracted according to the salting out procedure[30]. After extraction, the polymorphism was genotyped by use of polymerase chain reaction (PCR) and classified as DD, DI or Insertion/Insertion (II).

Statistical Analysis

All data obtained were analyzed by use of the statistical program Statistical Package for the Social Science for Mac (SPSS), version 21. In all tests, the rejection level of the null hypothesis was fixed as 0.05 or 5% ($p < 0.05$) and the 95% confidence interval (CI) was used. The central trend measurements were expressed as mean ± standard deviation.

The following tests were used: chi-square, Student *t* test and analysis of variance (ANOVA).

The genotype and haplotype frequencies were tested for Hardy-Weinberg equilibrium[31], by using the ARLEQUIN software, 2000 version.

The project was approved by the Committee on Ethics and Research of the Pedro Ernesto university-affiliated hospital (December 16th 2009). All patients provided written informed consent.

The present study was partially financed by the Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ) after approval of the Inovacor project.

Results

Genetic profile of the population studied

In the population studied, the D allele occurred 163 times (73%), while the I allele, 59 times (27%). Regarding genotypes, 57 (51.4%) were classified as DD, 49 (44.1%) as DI, and only 5 (4.5%) as II. The population studied was in Hardy-Weinberg equilibrium.

Characteristics of the population sample

There was a predominance of the male sex and white individuals, and a high incidence of systemic arterial hypertension (SAH) and smoking. However, the prevalences of diabetes mellitus and dyslipidemia were relatively low. No significant difference in the genotypes was observed for any of the clinical or laboratory characteristics assessed (Table 1).

The idiopathic etiology prevailed (36.0%), followed by the hypertensive (20.7%); however, there was no statistically significant difference in the distribution of the etiologies regarding the GPACE ($p = 0.248$).

A high percentage of use of major beta-blockers (BB), ACE inhibitors (ACEI) and/or angiotensin-receptor blockers (ARB) was observed, with mean doses close to those recommended by the current Brazilian Guidelines for Heart Failure[32]. There was no difference concerning the distribution of the type of drugs used according to the GPACE (Table 2).

Of the patients studied, 34 (30.6%) had QRS ≥ 120 ms, 38 (34.2%) had LBBB, and 22 (19.8%) had AF on ECG. The distribution of those variables according to the GPACE types was not statistically different.

Eight (7.2%) patients had implantable devices as follows: three (2.7%) had pacemakers; two (1.8%) had implantable cardioverter-defibrillators (ICD); two (1.8%) had undergone cardiac resynchronization therapy (CRT); and one (0.9%) had a combined device (ICD + CRT).

Echocardiographic outcomes

Approximately half of the cohort (49.5%) had severe LV systolic dysfunction when beginning follow-up, with LVEF ≤ 35%. That percentage increased to 58.5% by the end of the study.

Table 3 shows the echocardiographic data at the beginning and at the end of the study, and the evolution of such measurements. The means of the initial echocardiographic parameters (LVEF, LVSD and LVDD) did not significantly differ between the ACE genotypes. On final echocardiography, only LVSD was significantly different, with a lower mean for the DI GPACE.

Analyzing the evolutionary behavior of each echocardiographic variable [difference between the LVEF at the last and first consultation (ΔLVEF); difference between the LVSD at the last and first consultation (ΔLVSD); and difference between the LVDD at the last and first consultation (ΔLVDD)], the following distinct and significant patterns are observed: on average, DI showed an increase in LVEF as compared to the initial, while DD and II showed a decrease (Figure 1). Regarding the LV size, the DI genotype showed a reduction in LVSD and LVDD at the end of follow-up, while the DD and II genotypes showed an increase in the cavitary diameters (Figures 2 and 3, respectively).

The qualitative analysis (increase *versus* decrease) of the ΔLVSD (Figure 4) and of the ΔLVDD showed a difference between the GPACE with statistical significance for LVSD ($p = 0.046$), but not for LVDD ($p = 0.095$): the DD genotype had a greater number of patients with increased LVSD while the DI variant had a greater number of patients with decreased LVSD by the end of the study.

Discussion

This study describes the relationship between the GPACE variants and the clinical and echocardiographic outcomes in 111 patients with non-ischemic HF, with mean follow-up of 5.4 years (range, 12.0 - 249.7 months). Other international[11,13] and national[14,15] studies have carried out that analysis; however, this study is the first to assess exclusively non-ischemic HF in a Brazilian population with a mean follow-up time longer than five years.

Two findings of this study are worthy of note. First, the ACE genotypic profile of the population studied differed from that of most of previous publications, with an extremely low proportion of type II GPACE (only 4.5% of the patients). In addition, the echocardiographic evolutionary behavior represented by the variables ΔLVEF, ΔLVSD and ΔLVDD differed between the GPACEs, with worsening of those parameters in the DD genotype.

The low prevalence of the II genotype observed in this study can be related to the characteristics of the population studied, especially their ethnicity. The meta-analysis by Bai et al[4], with 2,453 cases of HF of multiple etiologies, included only 6.4% of black individuals and 23.4% of those of Asian origin, while the population of this study consisted of 51% of white individuals, 36% of black, 13% of individuals with mixed heritage and none of Asian ethnicity. The differences in the prevalences of the ACE genotypes found in this study and in the study by Bai et als. were, respectively: 51.4% *versus* 31% for DD; 44.1% *versus* 46% for DI; and 4.5% *versus* 23% for II.

Tiago et al[33], studying 157 black individuals with idiopathic HF in South Africa, have reported a GPACE distribution more similar to ours: 45.2% of DD; 38.2% of DI; and 6.5% of II. That might have resulted from the exclusive presence of Afro-descendants in that study. Velloso et al[10] have described a similar association of other GPs and the skin color of individuals with HF: the GP prevalences of nitric oxide synthase differed between white and Afro-American individuals.

The different etiologies of non-ischemic HF did not relate to the genetic profile, and the absence of patients with ischemic HF might not have determined higher or lower incidence of any of the genotypes. Amir et al[34], studying 195 patients with HF (124 ischemic and 71 non-ischemic), have already demonstrated no significant variation in genotypes regarding etiology.

Table 1 - Clinical characteristics of the population studied according to the genetic polymorphisms of the angiotensin-converting enzyme

Clinical variable*	Mean	DD (n = 57)	DI (n = 49)	II (n = 5)	Statistical test	p Value
Follow-up (months)	64.9 ± 3.9	65.2 ± 6.1	64.7 ± 5.1	63.6 ± 13.6	F = 0.004	0.996
HF duration (months)	97.0 ±6.9	89.9 ± 7.6	107.6 ± 12.7	73.4 ± 15.0	F = 1.067	0.348
Age (years)	59.5 ±1.3	61.1 ± 12.6	57.8 ± 14.6	57.2 ± 10.7	F = 0.852	0.429
Male gender	67 (60.4)	35 (61.4)	27 (56.3)	4 (80.0)	X^2 = 1.61	0.560
Ethnicity						
White	57 (51.4)	27 (47.4)	25 (52.1)	4 (80.0)		
Black	40 (36)	22 (38.6)	17 (35.4)	1 (20.0)	X^2 = 2.158	0.707
Others	14 (12.6)	8 (14.0)	6 (12.5)	0 (0)		
BMI (kg/m^2)	26.1 ± 0.6	26.0 ± 0.9	26.1 ± 0.8	28.0 ± 2.2	0.231	0.794
Arterial hypertension	78 (70.3)	41 (71.9)	33 (68.8)	4 (80.0)	X^2 = 0.338	0.845
Diabetes mellitus	24 (21.6)	13 (22.8)	9 (18.8)	2 (40.0)	X^2 = 1.267	0.531
Anemia	17 (15.3)	11 (19.3)	6 (12.5)	0	X^2 = 1.879	0.391
Dyslipidemia	43 (38.7)	23 (40.4)	17 (35.4)	3 (60.0)	X^2 = 1.228	0.541
Atrial fibrillation	22 (19.8)	12 (21.1)	8 (16.7)	2 (40.0)	$\chi 2$ = 1.751	0.781
Current smoker	7 (6.3)	8 (14.3)	3 (6.3)	2 (40.0)	X^2 = 7.350	0.775
Former smoker	45 (40.5)	24 (42.1)	19 (39.6)	1 (20.0)		
Current alcoholic	21 (19.1)	8 (14.3)	10 (20.8)	3 (60.0)	X^2 = 7.350	0.118
Former alcoholic	42 (38.2)	20 (35.7)	20 (41.7)	1 (20.0)		
initial NYHA** I	25 (22.5)	13 (22.8)	12 (25.0)	0 (0)		
initial NYHA** II	51 (45.9)	25 (43.9)	22 (45.8)	4 (80.0)	X^2 = 5.400	0.714
initial NYHA** III	23 (20.7)	14 (24.6)	8 (16.7)	1 (20.0)		
initial NYHA** IV	3 (9.9)	5 (8.8)	6 (12.5)	0 (0)		
mean initial NYHA	2.18 ± 0.09	2.19 ± 0.12	2.17 ± 0.14	2.20 ± 0.20	F = 0.012	0.988
final NYHA I	41 (36.9)	19 (33.3)	19 (39.6)	3 (60.0)		
final NYHA II	53 (47.7)	26 (45.6)	25 (52.1)	2 (40.0)	$\chi 2$ = 7.664	0.264
final NYHA III	14 (12.6)	11 (19.3)	3 (6.1)	0 (0)		
final NYHA IV	3 (2.7)	1 (1.8)	2 (4.2)	0 (0)		
mean final NYHA	1.81 ± 0.07	1.89 ± 0.10	1.76 ± 0.11	1.40 ± 0.25	F = 1.224	0.298
Hemoglobin (g/dL)	14.2 ± 1.3	12.57 ± 1.94	16.02 ± 20.28	14.2 ± 1.30	F = 0.834	0.437
Creatinine (mg/dL)	1.03 ± 0.18	1.03 ± 0.31	1.12 ± 0.18	0.40 ± 0.24	F = 0.336	0.715
Uric acid (mg/dL)	6.5 ± 0.2	6.51 ± 2.20	6.52 ± 2.01	5.2 ± 1.48	F = 0.92	0.402
Sodium (mEq/L)	138.9 ± 0.3	138.43 ± 3.60	139.40 ± 2.83	139.40 ± 2.41	F = 1.213	0.302
Potassium (mEq/L)	4.1 ± 0.1	4.18 ± 0.66	4.02 ± 0.64	4.00 ± 0.71	F = 0.817	0.445
Total cholesterol (mg/dL)	184.4 ± 4.6	187.4 ± 5.8	182.8 ± 7.7	165.8 ± 12.2	F = 0.511	0.602
EGFR (mL/min)	74.6 ± 3.8	74.9 ± 5.5	72.9 ± 5.3	101.5 ± 34.1	F = 0.707	0.497

**Numerical variables expressed as mean ± standard deviation; categorical variables, expressed as n (%); **there was no data on initial NYHA class for one Group DI patient. DD: deletion/deletion genotype; DI: deletion/insertion genotype; II: insertion/insertion genotype; Follow-up: follow-up duration (months); F: frequency; HF duration: disease evolution since disease diagnosis; BMI: body mass index; NYHA: New York Heart Association; EGFR: estimated glomerular filtration rate.*

The analysis of the echocardiographic variables showed a significant difference between the means of final LVSD according to the ACE genotypes. The DD GPACE showed higher means than the DI GPACE: 59.2 mm *versus* 52.3 mm, respectively. The small number of patients with the II genotype limited the analysis for that group. The evolutionary parameters ΔLVEF, ΔLVSD and ΔLVDD differed significantly between the GPACEs, with improvement in the EF and LV diameters (reverse remodeling) in the DI genotype. The DD and II genotypes

Table 2 - Medicamentous treatment of the Brazilian population studied according to the genetic polymorphisms of the angiotensin-converting enzyme*

Drug	Mean	DD (n = 57)	DI (n = 49)	II (n = 5)	Statistical test	p Value
Beta-blocker	108 (98.2)	55 (98.2)	47 (97.9)	5 (100.0)	$X^2 = 0.111$	0.946
Carvedilol	76 (71.0)	34 (61.8)	36 (78.3)	5 (100.0)		
Metoprolol	16 (15.0)	10 (18.2)	4 (8.7)	0 (0)	$X^2 = 7.471$	0.279
Bisoprolol	14 (13.1)	11 (20.0)	5 (10.9)	0 (0)		
Target dose	84.9 ± 3.7	84.3 ± 4.3	84.6 ± 5.8	91.2 ± 32.3	F = 0.78	0.925
ACEI	60 (54.1)	30 (52.6)	26 (54.2)	4 (80.0)	$X^2 = 1.394$	0.498
Captopril	6 (10.0)	3 (10.0)	3 (11.5)	0 (0)	$X^2 = 0.513$	0.774
Enalapril	54 (90.0)	27 (90.0)	23 (88.5)	4 (100.0)		
Target dose	66.7 ± 3.3	60.4 ± 5.9	71.6 ± 6.4	81.3 ± 1.9	F = 1.233	0.299
ARB: Losartan	39 (35.1)	22 (38.6)	14 (29.2)	2 (40.0)	$X^2 = 2.158$	0.707
Target dose	73.1 ± 4.3	80.7 ± 10.3	63.3 ± 8.4	62.5 ± 3.8	F = 0.574	0.569
Spironolactone	74 (66.7)	39 (68.4)	33 (68.8)	2 (40.0)	$X^2 = 1.771$	0.413
Furosemide	79 (71.2)	43 (75.4)	32 (66.7)	3 (60.0)	$X^2 = 1.274$	0.529
Mean dose (mg)	75.4 ± 5.7	80.5 ± 8.0	71.5 ± 8.7	46.7 ± 17.6	F = 0.791	0.457
Hydrochlorothiazide	26 (23.4)	14 (24.6)	12 (25.0)	-	$X^2 = 1.624$	0.444
Digitalis	40 (36.0)	25 (43.9)	13 (27.1)	1 (20.0)	$X^2 = 3.751$	0.153
Amiodarone	13 (11.7)	6 (10.5)	6 (12.5)	0	$X^2 = 0.746$	0.689
Statins	50 (45.0)	29 (50.9)	17 (35.4)	4 (80.0)	$X^2 = 5.033$	0.081
Allopurinol	18 (16.2)	9 (15.8)	7 (14.6)	1 (20.0)	$X^2 = 0.112$	0.946

**Numerical variables expressed as mean ± standard deviation; categorical variables, expressed as n (%). DD: deletion/deletion genotype; DI: deletion/insertion genotype; II: insertion/insertion genotype; F: frequency; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker.*

Table 3 - Echocardiographic parameters of the population studied according to the genetic polymorphisms of the angiotensin-converting enzyme

Variable*	Total mean	DD (n = 57)	DI (n = 49)	II (n = 5)	Statistical test	p Value
initial LVEF (%)	34.0 ± 1.0	35.6 ± 1.5	32.1 ± 1.5	34.6 ± 3.4	F = 1.469	0.235
initial LVSD (mm)	54.9 ± 1.0	54.1 ± 1.4	55.7 ± 1.4	55.4 ± 3.0	F = 0.472	0.625
initial LVDD (mm)	65.9 ± 0.9	65.6 ± 1.2	66.1 ± 1.3	66.6 ± 3.1	F = 0.112	0.894
final LVEF (%)	34.3 ± 1.2	32.8 ± 1.6	36.4 ± 1.8	29.4 ± 4.2	F = 1.634	0.200
final LVSD (mm)	56.1 ± 1.3	59.2 ± 1.8	52.3 ± 1.9	59.2 ± 5.2	F = 3.677	0.029
final LVDD (mm)	67.0 ± 1.2	69.4 ± 1.8	64.0 ± 1.8	69.0 ± 4.6	F = 2.197	0.116
ΔLVEF (%)	0.36 ± 1.37	-2.57 ± 14.86	4.62 ± 12.92	-5.20 ± 13.48	F = 3.857	0.024
ΔLVSD (mm)	0.94 ± 1.17	4.60 ± 12.04	-3.73 ± 11.28	3.80 ± 8.70	F = 6.783	0.002
ΔLVDD (mm)	0.82 ± 1.04	3.38 ± 9.90	-2.49 ± 11.47	2.40 ± 5.41	F = 4.026	0.021
Interval between exams (months)	65.5 ± 4.3	63.2 ± 6.3	68.0 ± 6.4	65.4 ± 12.4	F = 0.142	0.868

**Numerical variables expressed as mean ± standard deviation. DD: deletion/deletion genotype; DI: deletion/insertion genotype; II: insertion/insertion genotype; F: frequency; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic diameter; LVDD: left ventricular diastolic diameter; ΔLVEF: difference between the LVEF at the last and first consultation; ΔLVSD: difference between the LVSD at the last and first consultation; ΔLVDD: difference between the LVDD at the last and first consultation.*

showed an inverse behavior, with worsening of the EF and of the ventricular diameters (cardiac dilation).

That more severe evolutionary pattern related to the DD GPACE is in accordance with the findings of other authors[16,24]. The more marked cardiac dilation in those patients relates to the higher neuro-humoral activation, mainly of the RAAS. The GPACEs are responsible for approximately 50% of the variation in ACE levels, the DD genotype being associated with higher levels of that enzyme[35]. Elevated ACE levels are accompanied by

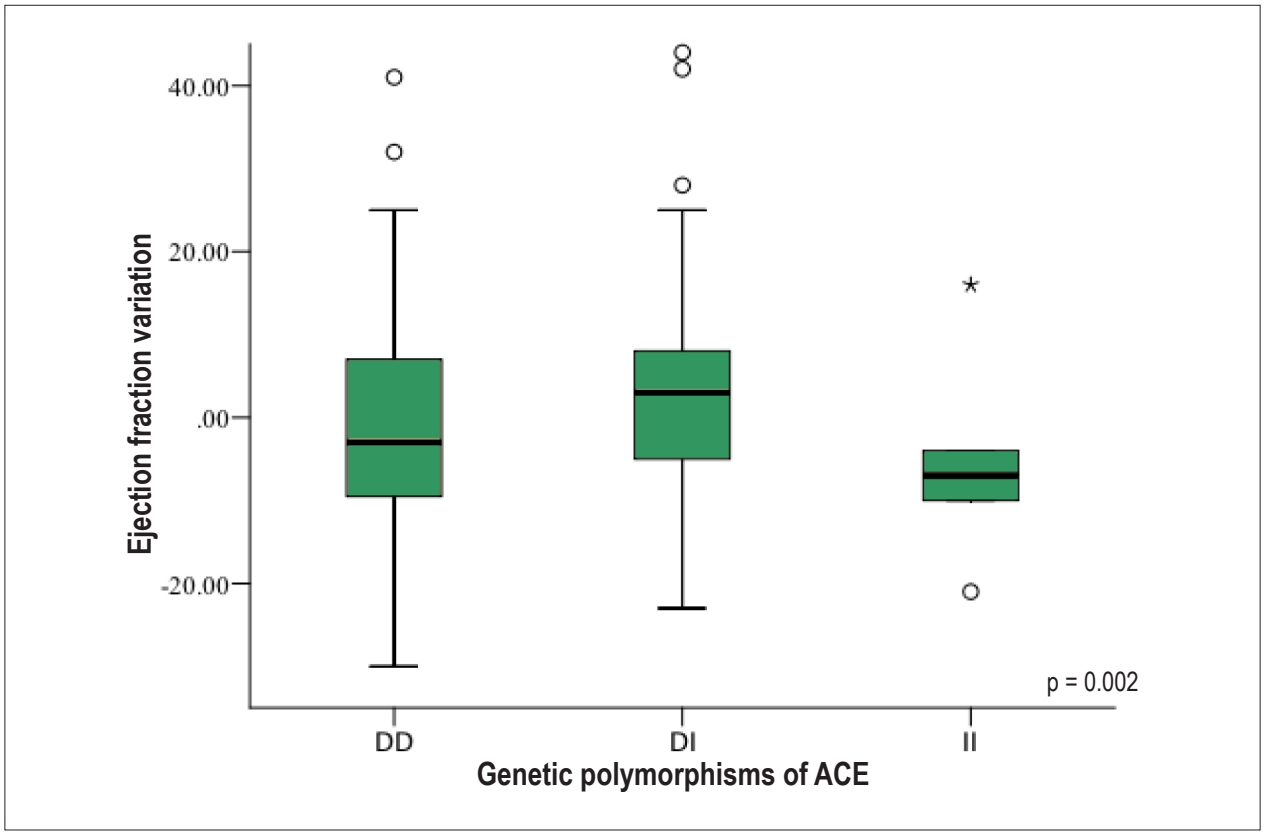

Figure 1 - *Ejection fraction variation between the end and the beginning of follow-up of the population studied according to the genetic polymorphisms of the angiotensin-converting enzyme (ACE). DD: deletion/deletion genotype; DI: deletion/insertion genotype; II: insertion/insertion genotype.*

increased synthesis of angiotensin and greater activation of that system[36].

However, those results are not uniform. De Groote et al[11] have found no difference in the echocardiographic parameters of 199 patients with HF, who had not initiated the BB use. The short interval between exams (only three months after optimization of the BB dose as compared to 65.5 months in this study) might have been insufficient to observe cardiac reverse remodeling in that study. Mahjoub et al[17] have not detected echocardiographic differences between the GPACEs, but those authors have chosen a categorical analysis, dividing the sample into two groups according to the LVDD (≥ 69 mm *versus* < 69 mm), corresponding to higher or lower severity, respectively. The statistical analysis of the present study used the numerical values of the echocardiographic parameters as continuous variables, having, thus, higher discriminatory power.

The clinical profile of each cohort varies between studies. In addition to the already discussed relationship of ethnicity and GPACE prevalence, other factors seem to influence the participation of the *ACE* gene on HF natural history and pathophysiology. One of the major factors is drug treatment.

The percentage of BB use was 98.2%, with a target dose of 84.3% of that recommended, higher than that of most clinical trials[14,18,20]. The use of ACEI and/or ARB was 91.2%, and that of spironolactone, 68.4%. However, the excellence of that treatment can interfere with the patients' clinical outcomes, hindering the observation of differences according to GPACE.

McNamara et al[12,13] have assessed the pharmacogenetic interaction, observing the use of BB[12] and ACEI[13] and the GPACEs. The DD genotype was associated with worse clinical and echocardiographic outcome, but the impact of that GP was attenuated by the treatment with BB and ACEI. In other words, for that group of patients, the neuro-humoral block might have neutralized the excessive RAAS activity secondary to the DD GPACE. Thus, under optimized therapy, the three genotypes, DD, DI and II, began to behave in a similar manner regarding clinical outcome.

In another study, the combination of two GPACE genetic variants with the GP in the angiotensin II receptor has shown an independent association with clinical outcomes[37].

Thus, the polygenic character described for other physical characteristics, such as height[38] or lipid profile[39], might also seem to play a role in the HF pathophysiology and in RAAS action. The simultaneous study of multiple GPs in the same population has identified that only combinations of genotypes have been associated with clinical and/or echocardiographic outcomes[19,20]. A panel of genetic markers might be more efficient in detecting more severely ill individuals than isolated GPs.

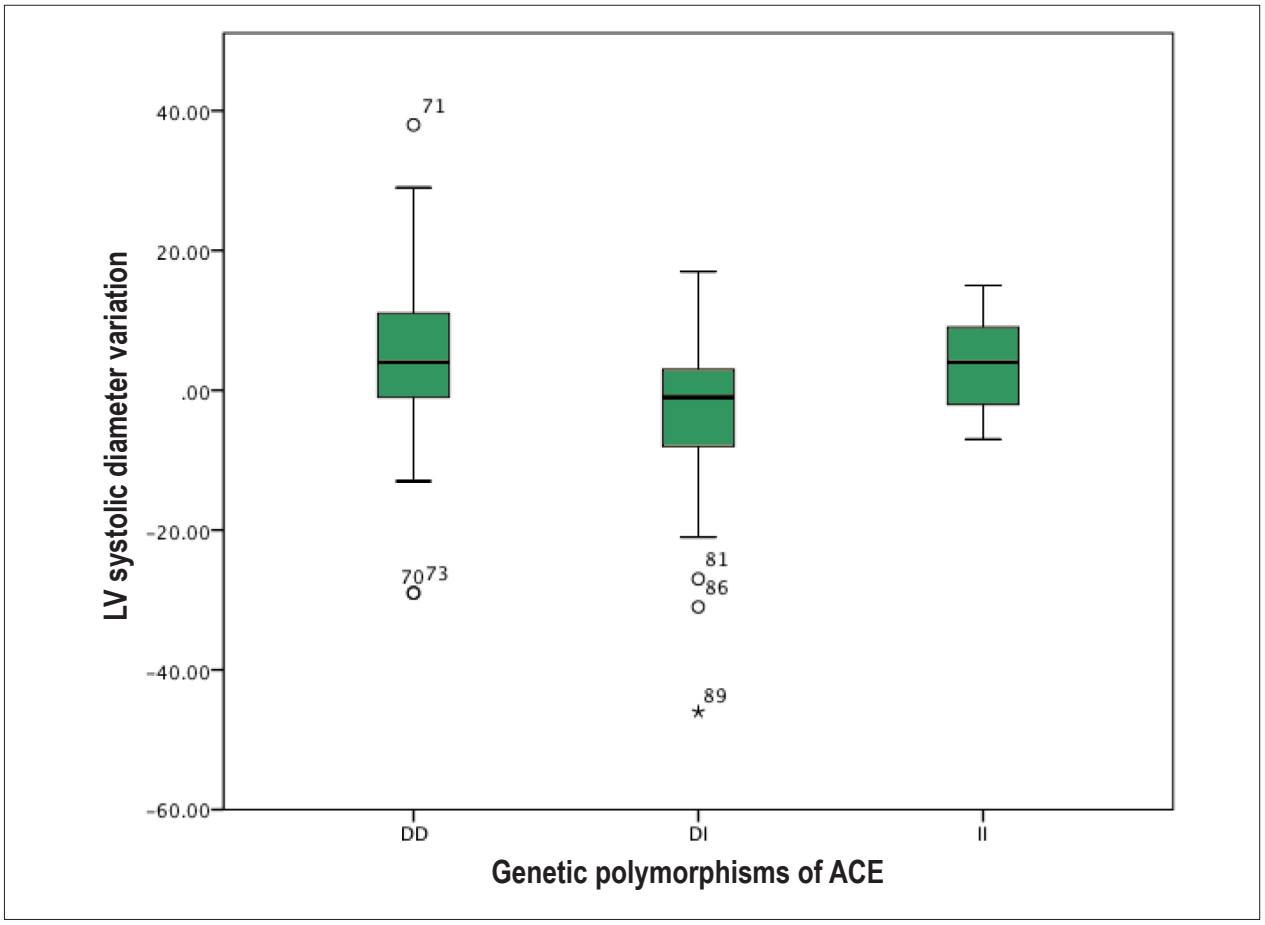

Figure 2 - *Left ventricular (LV) systolic diameter variation between the end and the beginning of follow-up of the population studied according to the genetic polymorphisms of the angiotensin-converting enzyme (ACE). DD: deletion/deletion genotype; DI: deletion/insertion genotype; II: insertion/insertion genotype.*

The present study has some limitations. First, the relatively small number of individuals studied, especially the reduced number of individuals with the II genotype, hindered a more conclusive data analysis. In addition, data collection from medical records represents, by definition, a limitation. However, it is worth noting that such limitation might have been attenuated by the high quality of the service provided at a well-structured HF clinic, with defined protocols, professional training and regular auditing. Last, because this is also a retrospective study, a selection bias might have occurred with the inclusion of a smaller number of more severely ill patients. However, the II genotype, theoretically more prevalent in less critical patients, had the lowest prevalence, which counteracts that selection bias.

The application of genetics to the HF context has become a potentially interesting and attractive tool for risk and severity stratification, as well as a marker of therapeutic response. The complex genetic architecture, represented by the already known polygenic heritage of other characteristics, illustrates the study difficulty on the subject. However, better understanding that area might have a great impact on medical practice, especially cardiology. Thus, the difficulties observed should not be seen as negative results, but as an incentive for further studies that would fill gaps and develop the knowledge in that important area.

Conclusion

The frequency of alleles and variants of GPACE has differed in most international and also national studies on HF, emphasis given to the small number of individuals with the II variant.

The echocardiographic parameters differed significantly between the GPACE variants. The DD genotype related to a worse echocardiographic outcome over a 5.4-year follow-up.

Author contributions

Conception and design of the research: Albuquerque FN, Brandão AA, Silva DA, Mourilhe-Rocha RM, Duque GS, Albuquerque DC; Acquisition of data: Albuquerque FN, Silva DA, Mourilhe-Rocha RM, Duque GS, Gondar AFP, Neves LMA, Bittencourt MI; Analysis and interpretation of the data: Albuquerque FN, Brandão AA, Silva DA, Pozzan R, Albuquerque DC; Statistical analysis: Albuquerque FN, Pozzan R; Obtaining funding: de Albuquerque FN, Albuquerque

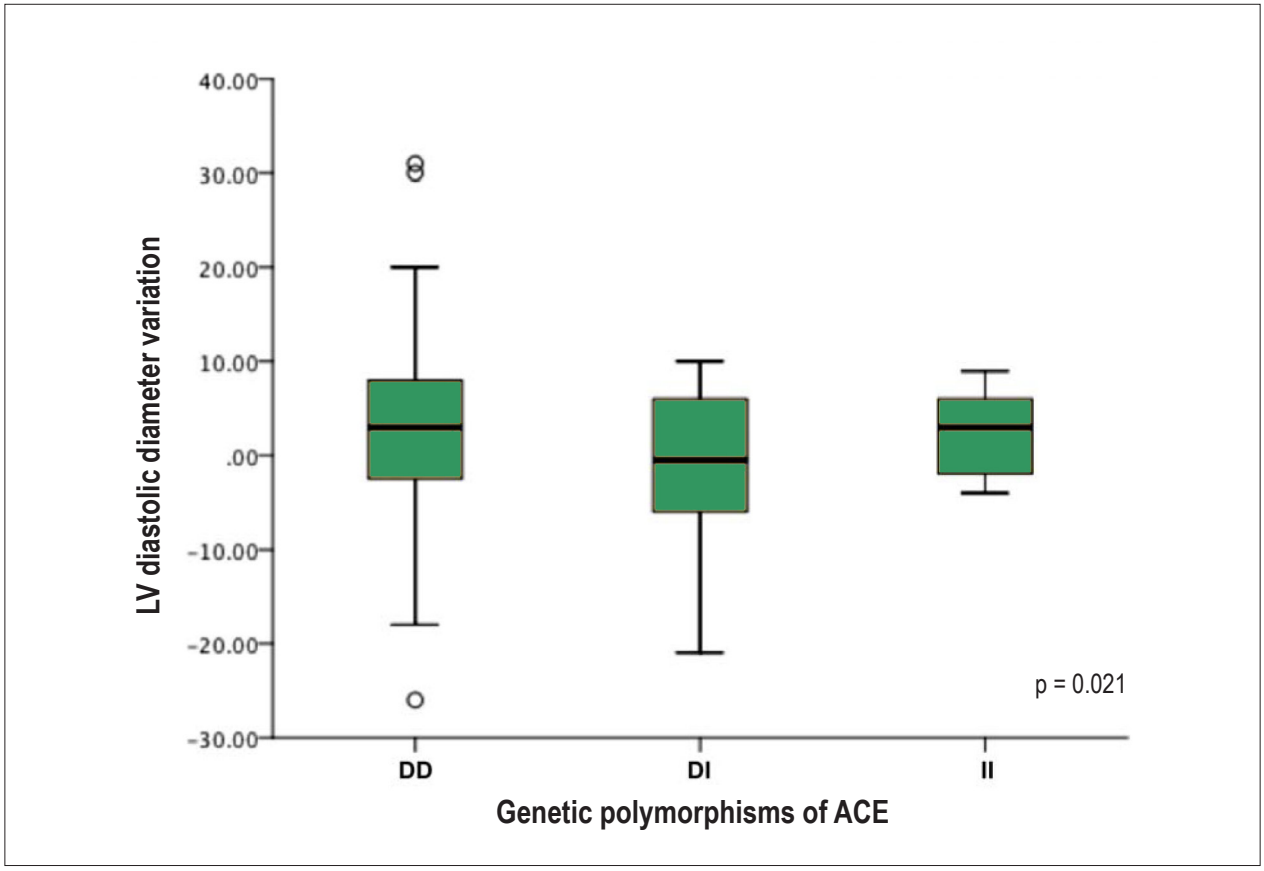

Figure 3 - *Left ventricular (LV) diastolic diameter variation between the end and the beginning of follow-up of the population studied according to the genetic polymorphisms of the angiotensin-converting enzyme (ACE). DD: deletion/deletion genotype; DI: deletion/insertion genotype; II: insertion/insertion genotype.*

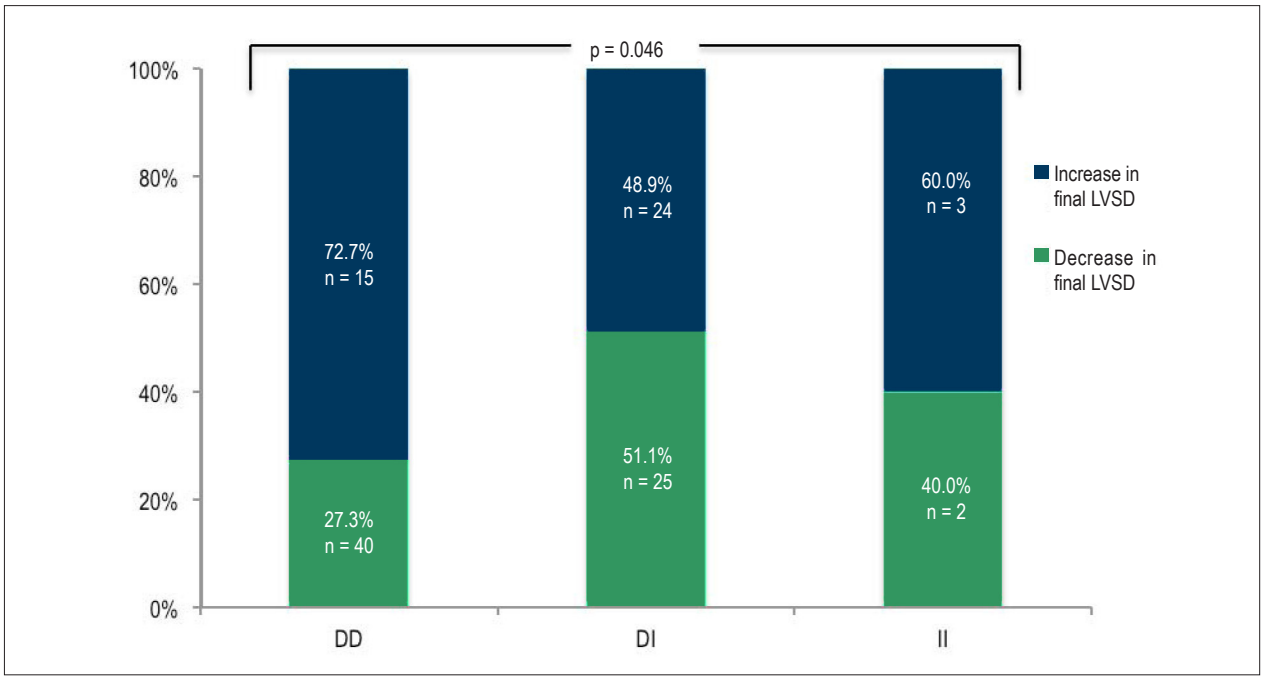

Figure 4 - *Evolutionary behavior of the left ventricular systolic diameter of the population studied according to the genetic polymorphisms of the angiotensin-converting enzyme (ACE). DD: deletion/deletion genotype; DI: deletion/insertion genotype; II: insertion/insertion genotype; LVSD: left ventricular systolic diameter.*

DC; Writing of the manuscript: Albuquerque FN, Brandão AA, Pozzan R, Albuquerque DC; Critical revision of the manuscript for intellectual content: Albuquerque FN, Brandão AA, Albuquerque DC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was partially funded by FAPERJ.

Study Association

This article is part of the thesis of master submitted by Felipe Neves de Albuquerque during the Post-Graduation in Medical Science of the Faculdade de Ciências Médicas of Universidade do Estado do Rio de Janeiro.

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