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Research Article

Progression of Left Ventricular Dysfunction and Remodelling under Optimal Medical Therapy in CHF Patients: Role of Individual Genetic Background

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Background. Neurohormonal systems play an important role in chronic heart failure (CHF). Due to interindividual heterogeneity in the benefits of therapy, it may be hypothesized that polymorphisms of neurohormonal systems may affect left ventricular (LV) remodelling and systolic function. We aimed to assess whether genetic background of maximally treated CHF patients predicts variations in LV systolic function and volumes. *Methods and Results*. We prospectively studied 131 CHF outpatients on optimal treatment for at least six months. Echocardiographic evaluations were performed at baseline and after 12 months. Genotype analysis for ACE I/D, β1adrenergic receptor (AR) Arg389Gly, β2AR Arg16Gly, and β2AR Gln27Glu polymorphisms was performed. No differences in baseline characteristics were detected among subgroups. ACE II was a significant predictor of improvement of LV end-diastolic and end-systolic volume ($P = .003$ and $P = .002$, respectively) but not of LV ejection fraction (LVEF); β1AR389 GlyGly was related to improvement of LVEF ($P = .02$) and LV end-systolic volume ($P = .01$). The predictive value of polymorphisms remained after adjustment for other clinically significant predictors ($P < .05$ for all). *Conclusions*. ACE I/D and β1AR Arg389Gly polymorphisms are independent predictors of reverse remodeling and systolic function recovery in CHF patients under optimal treatment.

1. Introduction

Chronic heart failure (CHF) is a major cause of morbidity and mortality [1]. Approximately 5 million Americans and more than 10 million Europeans have CHF, with an incidence approaching 1% of the population among people over 65 years of age [2]. It is a progressively debilitating condition and despite treatment, only half of the patients survive more than five years after diagnosis [3].

Left ventricular remodeling is a key process determining disease progression and affecting outcome in this condition. Several multicenter trials in patients with CHF have shown a survival benefit from the use of ACE inhibitors, beta-blockers, and aldosterone antagonists; such effects were associated with so-called reverse remodeling, in which the therapy promoted a return to a better left ventricular size and shape [4–7]. However, significant heterogeneity exists in the benefits to individual subjects. Great attention has therefore been devoted to the genetic makeup of the renin-angiotensin-aldosterone system (RAAS) and the beta-adrenergic system: understanding the functional role of these variants is a main aim of current research. One of the most comprehensively studied polymorphisms is ACE I/D, which is localized in the ACE gene. The DD genotype is implicated in numerous pathological conditions considered to be key risk factors for heart failure [8, 9]. Similarly, polymorphisms of β adrenergic receptors have been regarded as implicated in the variation of cardiac response to sympathetic drive. The aim of the present study was to assess whether the genetic background of the individual patient might predict changes

in left ventricular systolic function and volumes within a population of stable CHF outpatients under optimal medical treatment.

2. Methods

2.1. Study Population. A series of 148 consecutive outpatients with CHF was recruited from the Heart Failure Clinic of the Cardiology Department at Verona City Hospital. The local ethics committee approved the protocol and each patient gave written informed consent before participation in the study. The criteria for enrollment were a diagnosis of dilated cardiomyopathy of diverse etiology with a left ventricular ejection fraction <45%, stable clinical conditions, and optimal medical treatment at the maximally tolerated dosages according to the most recent CHF international guidelines for at least six months. All subject were followed up prospectively for one year and underwent two complete echocardiographic evaluations, at the beginning and at the end of followup.

2.2. Genotyping. A 2 mL blood sample was collected in an EDTA-containing tube and was kept at −80°C until the deoxyribonucleic acid (DNA) was isolated. We identified the following polymorphisms: ACE I/D, β1 adrenergic receptor (AR) Arg389Gly, β2AR Arg16Gly, and β2AR Gln27Glu. The gene polymorphisms studied were amplified using polymerase chain reactions (PCRs) and processed by restriction enzymes when needed. The procedure used to prepare DNA for PCR from whole blood was based on that described by Walsh et al. [10] for forensic material. Putative DD genotypes were further confirmed using the ACE 2 primer, which eliminates mistyping that can occur with a two-primer system. The PCR results were scored by two independent investigators unaware of patient identity. PCRs were run for 35 cycles: 30 seconds at 94°, 45 seconds at 56°, and 2 minutes at 72°. The product was subjected to electrophoresis in a 1.5% agarose gel and stained with ethidium bromide.

2.3. Statistical Analysis. Data were expressed by mean ± standard deviation (SD) for continuous variables or by number and percentage for categorical variables. Intergroup comparisons of % changes in left ventricular ejection fraction and volumes (% difference between end and beginning of followup: ΔLVEF, ΔLVEDV, ΔLVESV) were made using Student's *t*-test for unpaired data. Univariate and multivariate logistic regression analyses were used to determine the relationship between clinical and genetic variables and ΔLVEF, ΔLVEDV, and ΔLVESV. Commercially available statistical software was used (Statview 5.0, Abacus Concepts Inc; SAS 6.12, SAS Institute, Cary, North Carolina). A P value < .05 was considered statistically significant.

3. Results

3.1. Clinical Characteristics of the Study Population. During the observation period, six patients died, and one patient was lost to followup, while ten patients underwent implantation of a biventricular pacemaker, and were therefore excluded from further analyses because of the well-known resynchronization therapy effects on left ventricular remodeling and systolic function; 131 patients completed the study. The clinical baseline characteristics of study population are summarized in Table 1. Most patients were men, aged 63.2 ± 9 years old, and with a CHF of mainly ischemic (60.7%) or idiopathic origin (34.9%). At baseline mean left ventricular ejection fraction (LVEF) was 33 ± 7%, mean left ventricular end-diastolic volume (LVEDV) 266 ± 98 mL, and mean left ventricular end-systolic volume (LVESV) 181 ± 86 mL. No statistically significant differences in baseline characteristics were detected among the genotype subgroups.

Table 1: Baseline characteristics of study population.

Variable	
Age (yrs)	63.2 ± 9
Male gender *n* (%)	107 (82)
NYHA functional class	2.2 ± 0.7
SBP (mm Hg)	127 ± 15
DBP (mm Hg)	79 ± 8
Heart Rate (beats/min)	67 ± 11
S-Na^+ (mEq/L)	139 ± 3
S-Creatinine (μmol/L)	105 ± 25
Hb (g/dL)	13.9 ± 1.3
Treatment *n* (%)	
Diuretics	117 (90)
ACE inhibitors/ARBs	127 (97)
Beta blockers	110 (84)
Spironolactone	31 (24)
Statins	90 (69)
Echocardiography	
LVEF (%)	33 ± 7
LVEDV (mL)	266 ± 98
LVESV (mL)	181 ± 86
Genotypes, *n*	
ACE II/ ID, DD	20/111
β1 AR389 ≥1 Arg/GlyGly	31/100
β2 16 GlyGly/ ≥ 1 Arg	57/74
β2 27 GlnGln/ ≥ 1 Glu	51/80

Data are expressed as mean ± SD or number (%). Abbreviations: NYHA: New York Heart Association; SBP: systolic blood pressure; DBP: diastolic blood pressure; Hb: hemoglobin; ARBs: angiotensin II receptor blockers; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume.

3.2. Echocardiography. At one-year followup mean LVEF was 36 ± 9%; 8% of patients completely recovered their systolic function with an improvement of LVEF to a value >50%. We found that 45% of patients had a reduction of LVEDV > 10%, while only 21% increased their LVEDV >10%. A reduction of LVESV > 10% was found in 47% of subjects, whereas 25% of patients worsened, showing an increase in volume > 10%.

Association between Genetic Polymorphisms and Changes in LV Function and Volumes.. The relations between genetic

Table 2: Changes in echocardiographic parameters according to ACE and βAR genotypes.

		ΔLVEF	ΔLVEDV	ΔLVESV
ACE	II versus ID, DD	7/3	−16/0*	−19/0*
β1AR389	≥1Arg versus GlyGly	7/−7*	16/−3*	24/−6†
β2AR16	GlyGly versus ≥1Arg	0/6	−2/−3	−1/−5
β2AR27	GlnGln versus ≥1Glu	3/0	−3/−3	−4/−3

ΔLVEF (left ventricular ejection fraction), ΔLVEDV (left ventricular end diastolic volume), and ΔLVESV (left ventricular end systolic volume) are calculated as the percentage difference between followup and baseline left ventricular ejection fraction and volumes, respectively. Comparisons were made using the Student's t-test for unpaired data. *$P < .05$; †$P < .01$.

Table 3: Clinical predictors of ΔLVEF at one year follow-up (multivariate analysis).

Variable	P-value
Age (yrs)	.07
Nonischemic etiology	.006
NYHA functional class	.04
Diuretic dose (mg)	NS
S-Creatinine (μmol/L)	NS
Baseline LVEF (%)	<.0001

Abbreviations as in Table 1.

polymorphisms and variations in LVEF, LVEDV, and LVESV are described in Table 2. The ACE II genotype had a reduction of LVEDV and LVESV of 16% and 19%, respectively, while in ID/DD group there was no significant variation in left ventricular volumes over followup ($P < .05$ for both comparisons). β1AR389 GlyGly genotype was related to an improvement in LVEF of 7%, while the β1AR389 ≥ 1Arg group showed a decrease of 7% (intergroup comparison $P < .05$). Moreover, β1AR389 ≥1Arg was associated with a worsening of ventricular volumes with an LVEDV increase of 16% and an LVESV increase of 24%, whereas the β1AR389 GlyGly group showed a slight improvement of both LVEDV and LVESV ($P < .05$ and $P < .01$, resp., for intergroup comparisons). Genotypes of the β2AR 16 and β2AR 27 showed no significant changes in left ventricular systolic function or volumes over time.

3.3. Clinical Predictors of Remodeling. At the univariate analysis, significant predictors of improving LVEF were age ($P = .018$, $r = -0.13$), NYHA class ($P = .01$, $r = -0.15$), serum creatinine ($P = .01$, $r = -0.14$), diuretic dose ($P = .03$, $r = -0.12$), baseline LVEF ($P = .001$, $r = -0.22$), and nonischemic etiology ($P = .0003$). At the multivariate analysis, independent clinical predictors of improvement in systolic function were lower NHYA class, lower baseline LVEF, and nonischemic etiology (Table 3). Significant clinical predictors of changes in left ventricular volumes were systolic blood pressure, baseline LVEDV, and baseline LVESV, while at the multivariate analysis independent predictors of ΔLVEDV were only higher values of baseline LVEDV ($P = .0006$) and baseline LVESV ($P = .004$); systolic blood pressure was the only independent predictor of ΔLVESV ($P = .04$).

3.4. Genetic Predictors of Remodeling. ACE I/D was significantly correlated with ΔLVEDV and ΔLVESV, while we did not observe any association with ΔLVEF (Table 4). At the multivariate analyses it was significantly and independently related to both ΔLVEDV ($P = .03$) and ΔLVESV ($P = .028$), even after adjustment for baseline left ventricular volumes and systolic blood pressure. β1AR 389 was associated with both ΔLVEF and ΔLVESV, but not with ΔLVEDV. At the multivariate analyses it proved a significant predictor for both ΔLVEF ($P = .03$) and ΔLVESV ($P = .02$), even after adjustment for etiology, NYHA class, baseline values of LVEF, and LVESV and systolic blood pressure ($P < .05$ for both). β2AR 16 was only a borderline predictor of ΔLVEF at the univariate analysis, but lost its power at the multivariate analysis, while β2AR 27 was not associated with reverse remodeling or improvement in systolic function (Table 4).

4. Discussion

In the present study we analyzed the impact of genetic polymorphisms of the β adrenergic system and RAAS on ventricular remodeling and systolic function in a population of 131 CHF outpatients who had already been on optimal treatment for this condition for at least six months. Interestingly, at one year followup, we observed a significant improvement in left ventricular volumes and systolic function in about half and one fourth of patients, respectively. Importantly, along with clinical predictors of reverse remodeling and systolic function recovery such as baseline conditions and CHF etiology, we found that ACE I/D and β1AR 389 polymorphisms were independent predictors of functional and/or volumetric improvement, suggesting an important genetic background to disease progression and response to therapy. Because the benefits in terms of remodeling of beta blockers and ACE inhibitors are already evident after only three months of treatment [11, 12], to find an improvement after one year in subjects who had already been on optimal treatment for at least six months is a very remarkable result.

4.1. ACE Polymorphism. The ACE gene I/D polymorphism is one of the most comprehensively studied genetic variants in the field of cardiovascular disease. This polymorphism consists of the insertion (I) or deletion (D) of a 287-bp DNA fragment in intron 16 of the ACE gene. Serum and cardiac tissue levels of ACE and angiotensin II are related to ACE I/D polymorphism, with lower activation of RAAS in II subjects [13–15]. Previous studies report increased prevalence of DD genotype in CHF patients as compared with controls [16] and the same genotype is associated with increased mortality in patients with CHF [17]. In the present study we found that ACE gene polymorphism is a good predictor of left ventricular remodeling, being significantly, and independently related to both ΔLVEDV and ΔLVESV, even after adjustment for baseline values of volumes. The II genotype was significantly correlated

Table 4: Genetic predictors of echocardiographic changes at one year followup (univariate and multivariate analyses, see text for details).

Genotypes	Univariate analysis P-value			Multivariate analysis P-value		
	ΔLVEF	ΔLVEDV	ΔLVESV	ΔLVEF	ΔLVEDV	ΔLVESV
ACE II versus. ID/DD	NS	NS	.003	—	.03	.028
β1AR389 ≥ 1Arg versus GlyGly	.02	.02	NS	.03	NS	.02
β 2AR16 GlyGly versus ≥ 1Arg	.05	.05	NS	NS	NS	NS
β 2AR27 GlnGln versus ≥ 1Glu	NS	NS	NS	NS	NS	NS

Abbreviations as in Table 1.

with an improvement in left ventricular volumes, with a reduction of both LVEDV and LVESV. This observation is in accordance with previous studies from our group showing a genotype-dependent response to ACE-inhibitors and spironolactone in CHF patients [18, 19]. Nevertheless, even in the most unfavourable genetic conditions there is an important effect on disease progression of inhibition with maximal pharmacological therapy for CHF, as shown by the stability of left ventricular volumes in the majority of patients. Previous studies investigating the association between the ACE genotype and cardiac function in CHF patients assessed the negative impact of the DD group. McNamara et al. [20] evaluated the interaction between ACE inhibitor therapy and the effect of the ACE genotype on survival, finding that higher doses of ACE inhibitors diminished the impact of the ACE D allele. Our results further suggest the presence of a pathophysiological pathway from the ACE gene to increased levels of ACE and variations in cardiac function, supporting the hypothesis that ACE genotype modulates the progression and response to therapy in CHF.

4.2. β1AR 389 Polymorphism. The β1AR is the predominant β-adrenergic receptor expressed on the cardiomyocyte and is responsive to circulating epinephrine and to local norepinephrine derived from cardiac sympathetic nerves [21]. Two common polymorphisms of β1AR in the human population lead to either a glycine (β1AR Gly389) or an arginine (β1AR Arg389) at amino acid position 389, where the latter variation is characterized by increased function. The β1AR Arg389 polymorphism has been therefore considered a possible risk factor for heart failure, since it results in an increase of approximately 200% in agonist-stimulated activity in transfected cells as compared with the β1AR Gly389 receptor [22]. Its synergic effect with other polymorphisms has been estimated to represent some degree of increased risk of CHF, whereas the β1AR Arg389 genotype alone was not associated with heart failure [23]. In the present study we found that β1AR Arg389 genotype is an independent predictor of worsening systolic function and LVESV, while the β1AR Gly389 genotype was not associated with substantial changes.

Previous studies investigating the potential relationship between genotype and response to beta-blockers have reported contrasting results. Some have found no effect of beta adrenergic system polymorphisms on survival in CHF patients treated with beta blockers [24, 25]. Chen et al. [26] found that after treatment with carvedilol, patients with Arg/Arg genotype had a significantly greater improvement in LVEF compared to Gly389 carriers, whereas there were no differences attributable to other β1 and β2 adrenergic receptor polymorphisms. Taken together, these observations suggest that the β1AR Arg389 genotype could play a key role in promoting remodeling of the left ventricle, even in conditions of maximal medical therapy, and could identify patients at particularly high risk. Nevertheless, it should be said that this genotype characterises a minority of CHF patients, probably too few to allow extensive evaluation of the effect of the polymorphism on progression of CHF.

4.3. β2 Polymorphism. β2 receptors are also implicated in adrenergic signalling, even though norepinephrine released from sympathetic nerves shows a much lower affinity to these receptors than to β1. Our results revealed how β2AR Gly16 genotype is a borderline predictor for variation in LVEF (P = .05), while β2AR27 polymorphism is not significantly related to either systolic function or volumetric variation.

It is important to emphasize that in a highly progressive disease like CHF, most patients on standard treatment for this condition remained stable or even underwent a functional and volumetric improvement. Moreover, a significant percentage of patients had a complete recovery of systolic function. Many studies have already explored genotypes of RAAS and the adrenergic system as possible risk factors for CHF. In this research we rather analyzed how genetic background is related to progression of CHF, and found that functional and volumetric improvements were at least in part and independently related to genetic polymorphisms of neurohormonal systems. Understanding the mechanisms underlying the pharmacogenetic interaction between polymorphisms and treatment could predict which patients will respond best to beta-blockers and ACE inhibitors. Gene variation analyses will probably never completely prefigure drug responsiveness in a complex condition like CHF, but hopefully in the future they could help to select patients for treatment in a more specific way, evaluating ethnic and interindividual differences.

Our study has some limitations. The main one is the modest number of subjects in a few genotype groups. Because of the different frequencies of alleles in the population, several polymorphisms are difficult to recruit for investigation. To measure the impact of genetic variation in a multifactorial disease in which heterogeneous mechanisms and numerous interactions are implicated, larger trials are certainly needed. Moreover, analysis of the duration of the disease will be necessary, since the progression of CHF

and response to therapy are modulated by the grade of hypertrophy and interstitial fibrosis [27–29].

In conclusion, our results indicate that stable and maximally treated patients with CHF can improve their left ventricular systolic function and volumes according to specific baseline clinical and genetic variables. Some genetic variations may be more important in the progression of CHF than in its predisposition. Therefore, genetic polymorphisms could indeed be at least in part responsible for interindividual variation in progression of the disease as well as in response to therapy; whether genotyping may help to target therapy and improve clinical management of CHF patients can only be confirmed by large, randomized trials.

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Conflict of Interests

The authors declare that there is no conflict of interests to report.

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