

Adrenergic Receptor Polymorphisms in Heart Failure: What can Genetics Explain?

Sabrina Bernardez Pereira, Isabela Ambrósio Gava, Camila Giro, Evandro Tinoco Mesquita

Universidade Federal Fluminense, Rio de Janeiro, RJ - Brazil

Summary

Heart failure (HF) is a complex disease, which involves several physiopathological mechanisms and different genetic polymorphisms. The adrenergic system is directly related to this pathology, as it participates in cardiovascular autoregulation and has a crucial role in the deterioration of cardiac function. The beta-blockers appeared as a great advance in cardiology for the treatment of HF; however, the drug response varies according to each patient, as several factors are associated, such as the genetic one. This review aims at assessing the genetic involvement in the development of HF, the drug response and the prognosis.

Introduction

Currently, the clinical treatment for heart failure (HF) has a wide range of available drugs and beta-blockers are recommended for all stages of HF. However, there is great variability regarding response to treatment, with a survival rate that can vary from less than a year to more than 10 years.

In spite of the decrease in mortality, a significant number of patients from clinical trials do not benefit from the treatment with beta-blocker and 10% to 15% of the patients present adverse effects, which prevents their use.

The customized medicine is based on the identification of genetic variations that can predict the disease development and evolution and drug response (efficacy/safety). These variations represent the first genetic bases to determine the diagnosis, prognosis and therapeutic strategy guided by pharmacogenetics in HF.

The recent advances in molecular biology have facilitated the inclusion into clinical practice of tests that evaluate the polymorphisms in the cardiovascular area. One example is warfarin, with the approval by the Food and Drug Administration (FDA) of the rapid laboratory test to detect the CYP2C9 and VKORC1 polymorphisms, with the objective

of guiding the strategy of oral anticoagulation¹. Recently, the use of bucindolol in HF was approved in genetic testing to evaluate the Arg389Gly polymorphism, which will identify the individuals who will respond to this type of beta-blocker.

The objective of this review is to present the main scientific evidence of the role of polymorphisms of adrenergic receptors in the pathogenesis and progression of beta-blockers in HF and in their response to them.

Beta-adrenergic receptor polymorphisms

Studies on the adrenergic system have supported the hypothesis that genetic variants of the central or peripheral adrenoceptors have a role in the physiology of cardiovascular diseases, such as arterial hypertension and heart failure².

The family of beta-adrenergic receptors (β_1 , β_2 and β_3) is highly polymorphic. Recently, several functionally relevant polymorphisms of α_2 , β_1 and β_2 ADR receptors, and their specific genotypes were associated with the incidence and clinical severity of heart failure.

There are seven common polymorphisms for the adrenergic receptors (two for beta-1 and three for beta-2, one for beta-3 and one for alpha-2c), which will be analyzed regarding their involvement in the pathogenesis, therapeutic response and prognosis of HF (Figure 1)^{3,4}.

Beta-1 adrenergic receptor polymorphisms

The beta-1 adrenergic receptor gene is located at chromosome 10q 24-26. This gene has a codon sequence that codifies a protein with 477 amino acids intercalated by an untranslated region containing 86 base pairs in the extremity 5' and an untranslated region containing 900 base pairs in extremity 3'.

Eleven single-nucleotide polymorphisms (SNPs) have been described for the beta-1 gene, of which 8 result in amino acid change in the receptor. Two of these SNPs are the most common ones and are to date the most often described SNPs in literature.

The position 1165 of the gene can be occupied, more frequently, by a cytosine or by a guanine, alternating the amino acid at position 389 of the protein, in the carboxy-terminal extremity between Arginine (Arg) and Glycine (Gly), respectively. As for the position 145 of the gene, it is more frequently occupied by an adenine, or, less frequently, by a guanine, altering the amino acid at position 49 of the protein, in the amino-terminal extremity, between serine (Ser) and Glycine (Gly), respectively (Figure 2)^{5,6}.

Key words

Polymorphism, genetic; receptors, adrenergic; heart failure.

Mailing address: Sabrina Bernardez Pereira •

Rua Professor Otacílio, 94/601 - Santa Rosa - 24240-670 - Niterói, RJ - Brazil
E-mail: sbernardez@cardiol.br, s.bernardez@globo.com

Manuscript received December 31, 2008; revised manuscript received May 06, 2009; accepted August 19, 2009.

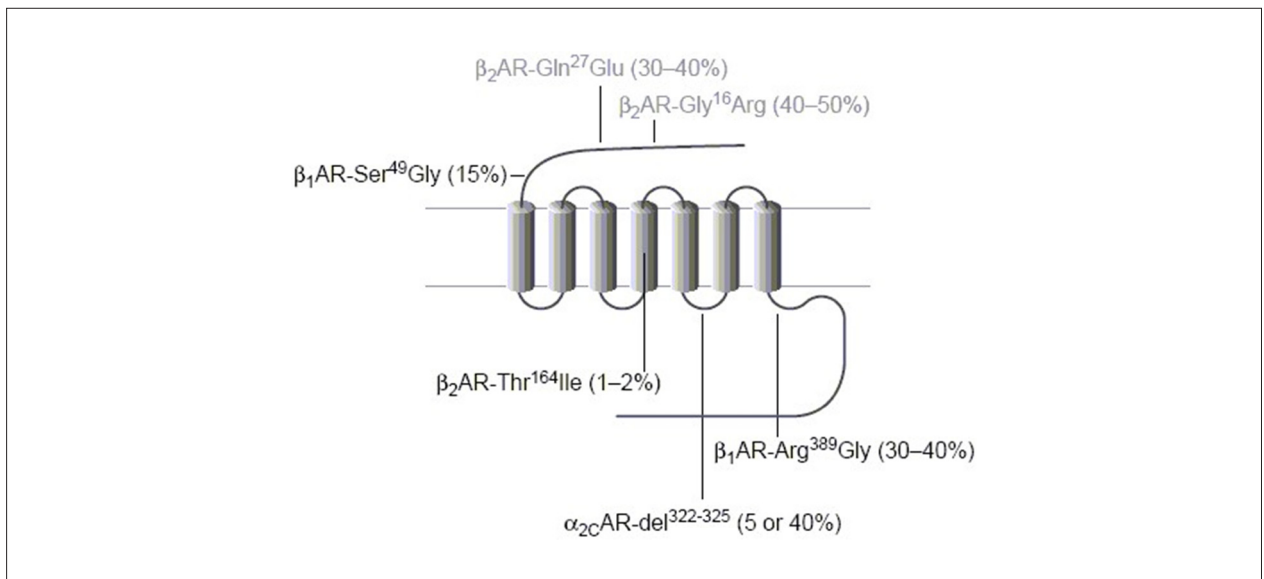


Figure 1 - Adrenergic system polymorphisms.

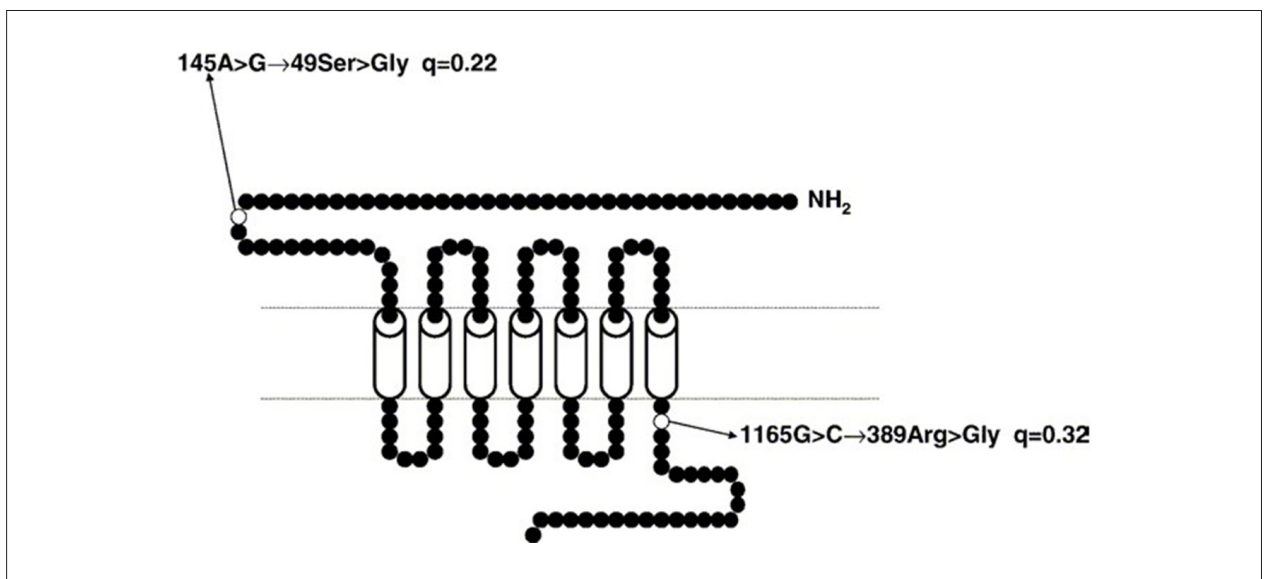


Figure 2 - Beta-1 receptor polymorphisms. q - allelic frequency (NCBI).

Among the other SNPs described for the beta-1 adrenergic receptor, are: Ala59Ser, Arg318Ser, Lys324Arg, Ala343Thr, Glu352Asp, Arg399Cys, Arg400Leu, His402Arg, Thr404Ala and Pro418Ala. However, these polymorphisms are rare (frequency of 1% to 2%), and there are not many studies about them^{7,8}.

Arg389Gly

The amino acid at position 389 of the beta-1 adrenergic receptor is located close to the seventh transmembrane domain, in the intracytoplasmic tail and it is supposed to be a G_s-protein binding domain⁶.

When this polymorphism was cloned for the first time, the allele present was Gly389, and, therefore, this allele was considered to be the wild-type allele for a long time, although it was less frequent⁹. The Arg389 allele is highly conserved among species, which suggests that it is the ancestral allele⁷.

The allelic prevalence is of approximately 70% for beta-1 Arg389 and 30% for beta-1 Gly389¹⁰. The frequency of the Gly allele in Caucasians and Asians is 27%, whereas the frequency in African-Americans is of 42%¹¹. The knowledge of the frequency of polymorphisms in different ethnic groups is relevant, as different genotypes are related to susceptibility,

response to therapy and distinct prognosis in cardiac diseases, as demonstrated by several studies.

Ser49Gly

At the amino terminal extremity of the beta-1 adrenergic receptor, in the extra-cytoplasmic domain, is the amino acid at position 49. The change in the amino acid at this position can alter the conformation of the transmembrane and intracytoplasmic portions of the protein. Moreover, it has a role in the catecholamine signaling and down-regulation of this receptor^{2,12}.

The Ser49Gly polymorphism is in linkage disequilibrium with Arg389Gly in Caucasians and African-Americans and all homozygotes for Gly389 are also homozygotes for Ser49 (Figure 3)⁹. This disequilibrium was demonstrated in a study with 700 women, in which only three of the four genotypic possibilities were found when 1,254 alleles were analyzed. The Gly49/Gly389 genotype was the only one that was not found⁵.

Allelic frequency

There is no statistically significant difference regarding the prevalence of the Gly49 allele in Caucasians and Asians and this frequency is 15% in both populations. Among African-Americans, different genotypic frequencies were identified by two groups. Johnson and Terra found a frequency of 29% for the Gly49 allele, whereas Moore et al¹³ observed a frequency of 13% of the same allele^{11,13}.

The functional role of polymorphisms in the beta-1 adrenergic receptors

In vitro experiments have demonstrated that the Arg389 allele is related to a slightly higher basal sympathetic activity than the one presented by the Gly389 allele. Additionally, β 1-Arg389 presents a faster desensitization, has higher affinity for the G_s protein and produces an activation of the effector enzyme adenylyl cyclase that is three-fold higher than the one induced by the Gly389 allele^{4,14}.

Experiments carried out in rats have shown that the Arg variant is related to a higher and better signaling in acute stages, but it becomes decreased chronically, with lower receptor-binding capacity. These same studies demonstrated that this

variant is related to an improvement in the hemodynamic activity and ventricular function in response to beta-blocking, which demonstrates the importance of such studies for the development of more effective and personalized therapies¹⁵.

The functional meaning of this amino acid change is mainly in the control of the beta-1 adrenergic receptor desensitization. The Ser49 variant is relatively more resistant to down-regulation than the Gly49, as it is more glycosylated, presenting higher levels of expression, particularly in diseases where the sympathetic activation is increased. As demonstrated by prior studies of G-protein binding receptors, the level of the protein N-glycosylation influences the desensitization, at the prolonged exposure to agonist as well as at the short exposure¹¹.

It was verified, however, that the polymorphism at position 49 does not seem to have an effect on ligand binding, G-protein binding or internalization promoted by the exposure to agonist. Actually, although the rate of internalization of both receptors is the same, there is 25% more degradation of the Gly49 receptor, favoring the down-regulation¹¹.

Although there is a consensus regarding the polymorphism at position 389 regarding its influence in the adenylyl cyclase activation, the same cannot be said of polymorphism Ser49Gly. Rathz et al¹² did not find, in their experiments, differences in the levels of activation of the adenylyl cyclase enzyme among the variants. However, Levin et al¹⁶ demonstrated that, when the density of the receptors was increased 10-fold, the cells that expressed Gly49 had an increased basal and agonist-dependent activity for the adenylyl cyclase. Additionally, Gly49 was more sensitive to the antagonists such as metoprolol and presented increased affinity for the agonists^{16,17}.

Susceptibility to heart failure

Considering the alterations that genetic variations of beta receptors can cause in the adrenergic system function and their impact on the predisposition to diseases and the therapeutic response, these polymorphisms have been related to the propensity to, evolution and outcome of several cardiac diseases and among them, heart failure (HF).

As described before, the Arg389 allele has a higher stimulating effect on the sympathetic system, whereas the Gly389 allele presents an increase of the down-regulation as a protective effect to the increased sympathetic activity in HF. Therefore, several studies have been developed to verify whether there is a correlation between the beta-1 polymorphisms and susceptibility to HF. In most studies, no statistically significant differences were found regarding the isolated frequencies of the Arg389 and Gly389 alleles in patients with HF, when compared to controls.

Exercise capacity in HF

When the Gly and Arg alleles are compared at position 389 with the capacity to perform physical exercises in HF, those carrying the Gly allele presented a better performance, although there was a similar increase in heart rate and blood pressure at maximum exertion². Wagoner et al¹⁸ evaluated 263 patients with dilated cardiomyopathy and demonstrated that individuals homozygous for Arg389 had a significantly

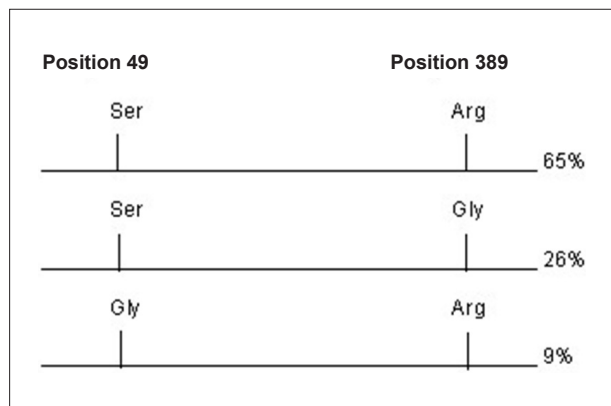


Figure 3 - Beta-1 adrenergic haplotype frequencies.

higher VO₂ peak. That suggests that the early detection of polymorphisms can identify those with lower physical capacity, and thus, direct individualized exercise programs¹⁸.

As for the Ser49Gly polymorphism, the sample population was not controlled for this codon alone. However, it was observed that this polymorphism can modulate the functional responsiveness of codon 389. Therefore, it is verified that the analysis of the haplotype must also be carried out and perhaps, it might be more important than the study of the SNPs alone¹⁷. In patients with HF, the Ser49/Gly389 haplotype presented lower VO₂ peaks, whereas patients carrying Gly49/Arg389 presented better VO₂ peaks.

Response to beta-blocker and prognosis in HF

In the last ten years, beta-blockers (metoprolol, bisoprolol and carvedilol) have been associated with a significant decrease in all causes of mortality and hospitalization of patients with HF, being recommended by the guidelines as the standard therapy. However, as demonstrated in the Merit-HF, there was a decrease in mortality of only 34% of the patients using metoprolol, when compared to placebo¹⁹. Such fact was determinant to justify the studies with the polymorphisms with the objective of identifying patients that respond to such therapy, taking into account the interindividual variations.

Terra et al evaluated 61 patients with systolic dysfunction and ejection fraction (EF) < 40%, titrating the dose of metoprolol up to 200 mg/d or the maximum tolerated dose. At the echocardiographic follow-up, after three months of medication use, these authors observed that patients homozygous for Arg389Arg presented a better EF response, with decreased systolic and diastolic cavity diameters, in comparison to those carrying the Gly allele^{20,21}.

The BEST study evaluated the use of non-selective beta-blocker (bucindolol) for the treatment of HF-functional class III-IV. The BEST-Genetic sub-study analyzed the impact of the beta-1 adrenergic polymorphism on the treatment with beta-blocker and verified a considerable improvement in survival and decrease hospitalization rate in patients homozygous for Arg389Arg, in contrast to those carrying the Gly allele³.

However, the results of the sub-study of the Merit-HF study with 600 patients did not confirm that the different responses to the beta-blocker use were associated with these polymorphisms²².

Terra et al^{20,21} observed that those carrying Gly49 presented a significant improvement in the degree of left ventricular remodeling after treatment with metoprolol, when compared to individuals homozygous for Ser49Ser. Moreover, these authors verified that the Arg389Arg genotype does not affect the tolerance to metoprolol at the initial phase of the titration, whereas patients carrying the Gly389 allele and homozygous for Ser49 presented higher levels of decompensation, indicated by the concomitant increase of other medications for HF^{20,21}.

Börjesson et al²³, evaluated 184 patients treated for long periods with beta-blockers and verified that those carrying 1 or 2 Gly49 alleles presented better improvement in 5-year survival than those homozygous for Ser49Ser, who had a higher probability of presenting the following outcomes: hospitalization, heart transplant and death.

In a prospective study with 375 patients with HF, Magnusson et al²⁴ demonstrated that the influence of codon 49 on the prognosis and treatment with beta-blockers is more pronounced than that of codon 389. Thus, patients carrying 1 or 2 Gly49 alleles treated with low-dose beta-blocker presented a lower rate of mortality than patients homozygous for Ser49.

Studies with the Arg389Gly polymorphism did not show an association with the survival rate¹⁵. However, that occurs when there is linkage disequilibrium between codons 49 and 389. Patients carrying the Gly49 variant almost always carry Arg in codon 389, whereas those carrying Ser49 might carry Arg or Gly in codon 389.

Table 1 summarizes the main effects of the beta-1 adrenergic receptor polymorphisms on prognosis and the response to beta-blockers in HF.

Adrenergic beta-2 receptor polymorphisms

The adrenergic beta-2 receptor is codified by a gene without introns and located in chromosome 5q31-32. To date, 12 SNPs (single-nucleotide polymorphisms) have been described for the beta-2 receptor gene. Of these, 5 (Arg16Gly, Gln27Glu, Trh164Ile, Val34Met and Ser220Cys) cause alterations in the receptor amino acids and have functional significance (Figure 4). The consequences of the Ser220Cys polymorphism are yet to be understood and it is estimated that the Val34Met polymorphism, which is quite rare, does not cause changes in the beta-2 receptor function. The others have shown to be associated with functional alterations of the receptor.

Arg16Gly

The substitution of cytosine by guanine in position 46 of the beta-2 gene determines the substitution of Arginine (Arg) by Glycine (Gly) in codon 16.

At the start of the investigations on the Arg16Gly polymorphism, it was believed that Arginine was the most frequent allele in the population (wild-type allele). However,

Table 1 - Beta-1 adrenergic receptor polymorphisms and their effect on the prognosis and the response to beta-blockers in HF

Polymorphism	Effect	Study
Arg389Gly	Arg389Arg>Gly389Gly: ↑ EF after 3 months of metoprolol use.	Terra et al
Arg389Gly	Arg389Arg >Gly389Gly: improvement in survival and hospitalization with bucindolol use.	Best-Genetic
Arg389Gly	Arg389=Gly389: response to beta-blockers.	Merit-HF sub-study
Ser49Gly	Gly49 > Ser49Ser: improvement in LV remodeling with metoprolol use.	Terra et al
Ser49Gly	Gly49 >Ser 49Ser: improvement in 5-year survival with beta-blocker use.	Börjesson et al
Ser49Gly	Gly49 > Ser49Ser: lower mortality rate with low beta-blocker dose.	Magnusson et al

EF - ejection fraction; LV - left ventricle

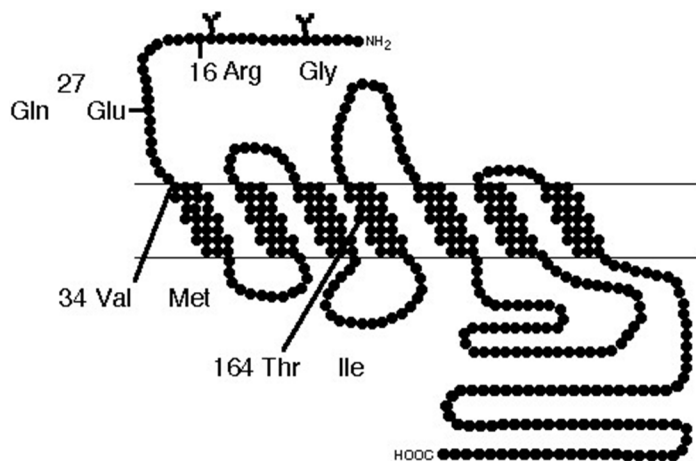


Figure 4 - Beta-2 receptor polymorphisms.

subsequent studies demonstrated that Glycine was actually the most frequent allele (Arg/Gly, allelic frequency 0.40/0.60). However, as it was originally described that way, the Arginine allele maintained the “wild-type” denomination and the Glycine allele maintained the “mutant” allele denomination².

Gln27Glu

The substitution of the adenine nucleotide by the guanine nucleotide at position 79 of the beta-2 adrenergic receptor gene results in the substitution of the glutamine amino acid by glutamic acid in codon 27. The glutamine allele, as it is more frequently found in the population, is called the “wild-type” allele. The glutamic acid, as it is less frequently found in the population, is called the “mutant” allele (Gln/Glu, allelic frequency 0.55/0.45)².

Trh164Ile

The presence of a different nucleotide at position 491 of the gene will determine the presence of a different amino acid in codon 164 (Trh164Ile)¹⁷.

Arg16Gly/Gln27Glu

It is currently known that there is a remarkable linkage disequilibrium between codons 16 and 27, so that individuals who are homozygous for Glu27Glu almost always present the Glycine amino acid in homozygosis in codon 16 (Gly16Gly). The homozygote Gln27Gln individuals can be homozygous (Arg16Arg or Gly16Gly) or heterozygous (Arg16Gly) for codon 16. The Arg16Glu27 haplotype is found in less than 1% of the population and, therefore, it is very rare¹¹.

Allelic frequency

The frequency of the alleles involved in the beta-2 receptor polymorphisms varies among different ethnic groups. In African-Americans, the frequency of the Arg16 allele is 49%, whereas, in Caucasians and Asians, it is 46% and 59%, respectively.

Regarding the Glu27 allele, the allelic frequency is 20% among African-American individuals. In Caucasians and Asians, the allelic frequency of Glu27 is 35% and 7%, respectively.

The frequency of Ile164 in Caucasians and African-Americans is 2% to 4%; in Asians, it is 0% to 1% and in Latin-Americans, 3%^{25,26}.

The functional role of beta-2 adrenergic receptor polymorphisms

It is well established that polymorphisms in codons 16 and 27 do not alter the binding capacity of catecholamines to beta-2 receptor and adenylyl cyclase activity. However, studies have demonstrated that these polymorphisms are strongly associated with the susceptibility of these receptors to the down-regulation phenomenon¹⁷.

In vitro studies have shown a higher degree of desensitization in the Gly16 variant in relation to the Arg16 variant, after the administration of isoprenaline. The same experiment also indicated that the Glu27 variant, as it causes an alteration in the conformation of beta-2 receptor, presents a higher degree of resistance to the down-regulation phenomenon than the Gln27 variant²⁷. Therefore, it is presumed that the Glu27 polymorphism produces a beta-2 receptor with a higher degree of responsiveness to adrenergic agonists². The Gly16Glu27 haplotype demonstrated to be more susceptible to the down-regulation phenomenon when compared to the Gly16Gln27 haplotype. One hypothesis for this fact would be the prevalence of the effect of Gly16 on the effect of the Glu27 variant. The Arg16Glu27 haplotype is the one that presents higher resistance to desensitization²⁸.

In vivo, three haplotypes have been studied: Arg16Gln27Thr164, Gly16Glu27Thr164 and Gly16Gln27Thr164. After two weeks of oral treatment with isoprenaline the Gly16Glu27Thr164 haplotype was the one that presented lower desensitization^{29,30}. In other studies, the intravenous treatment with isoprenaline resulted in higher desensitization of the Arg16Gln27Thr164 haplotype^{31,32}.

These results, which indicate a lower resistance of Arg16 to the down-regulation phenomenon, are different from the *in vitro* results. A possible hypothesis for that would be the exposure of the beta-2 adrenergic receptors to a basal level of endogenous catecholamines in a human model, which would allow a higher endogenous desensitization of Gly16. Thus, when exposed to an exogenous agonist, the Gly16 polymorphism, already desensitized, would present lower susceptibility to the down-regulation phenomenon³³.

Susceptibility to HF

Many studies have investigated a possible association between heart failure and the beta-2 adrenergic receptor polymorphisms and different results have been described in the literature. It is known that the proportion between beta-1 and beta-2 receptors is 80:20 in healthy hearts. However, in HF, this proportion is 60:40, which indicates that the beta-2 polymorphism can modify the disease progression¹¹.

Heckbert et al³⁴ carried out studies in a sample with more than 5,000 elderly individuals aiming at finding a possible association between the Arg16Gly and Gln27Glu polymorphisms and the risk of developing cardiovascular diseases. The results suggest that the individuals carrying the Glu27 allele present a lower risk of developing coronary events than the patients carrying the Gln27 allele in homozygosis.

Forleo et al³⁵, in their studies, concluded that Gly16Glu27 patients with dilated cardiomyopathy presented a higher risk of developing heart failure than Gly16Gln27 patients^{17,35}. However, as for the beta-1 polymorphism, there does not seem to be a significant difference between the allelic frequency of beta-2 receptors in patients with and without HF, which indicates that this polymorphism must not be associated with susceptibility to this disease. Covolo et al³⁶ did not find significant differences in the distribution of different alleles between patients with HF and controls^{17,36}.

Two studies have demonstrated that the frequency of the Ile164 polymorphism is similar between healthy patients and those with HF and concluded that this polymorphism is not a risk factor for HF, either^{37,38}.

Exercise capacity in HF

Some studies have verified the association between the different polymorphisms of beta-2 receptor and the capacity to perform physical exercises.

Wagoner et al¹⁸, after determining the genotype of 230 outpatients with HF, submitted them to cardiopulmonary exercise tests. The results showed that the individuals homozygous for Gly16 presented worse VO₂ peaks, when compared to individuals homozygous for Arg16. Moreover, when the genotypes of positions 16 and 27 were simultaneously evaluated, the Gly16Gln27 homozygotes were the ones that presented worse performance, with the best performance being associated with the individuals homozygous for Arg16Glu27⁹.

As for the patients with HF and Thr164Ile, they had a lower VO₂ peak ($15.0 \pm 0.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) than the ones presenting Thr164Thr ($17.9 \pm 0.9 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, $p < 0.0001$). The

percentage of the reached O₂ peak was also lower in patients with Ile164Thr ($62.3 \pm 4.5\%$ vs $71.5 \pm 5.1\%$, $p = 0.045$)¹⁸.

The exercise tests with Swan Ganz catheter measurements demonstrated lower variations in cardiac index, systemic vascular resistance, systolic volume and O₂ in Ile164 patients.

Response to beta-blockers and prognosis in HF

Regarding the response to medications, studies have shown that Arg16 and Glu27, when in homozygosis, promote a higher degree of vasodilation in response to adrenergic agonists. In turn, *in vivo* studies have demonstrated that the combinations of the Arg16 and Gln27 alleles showed the highest degree of desensitization measured by the agonist during the vasodilation response¹¹.

Studies carried out by Kayne et al³⁹ that assessed patients with HF treated with beta-blockers indicated that the risk of death of heart transplant was significantly higher in individuals that carried the Arg16Gln27 haplotype. When the Gln27 polymorphism was analyzed alone, patients that were homozygous for this allele showed little improvement in cardiac function when they received carvedilol, when compared to those carrying the Glu27 allele. These results were confirmed by Metra et al. At the time, the patients with chronic HF were treated for more than one year with carvedilol and it was verified that the left ventricular ejection fraction (LVEF) in individuals that were homozygous for Glu27 was much higher than in individuals homozygous for Gln27. No statistical significance was observed in studies that tried to correlate the response to carvedilol and the Arg16Gly polymorphism alone. However, due to the linkage disequilibrium, patients homozygous for Glu27 that presented better response to carvedilol are almost always carriers of the Gly16 allele in homozygosis^{17,39,40}.

De Groote et al⁴¹, in their experiments, observed in patients with the Gly16Gln27 haplotype a tendency to lower survival, when compared to patients with the two other haplotypes, demonstrating, once more, that the analysis of the SNPs alone might not be enough to characterize the disease evolution and that perhaps more studies are necessary before one can establish an association between beta-2 polymorphism and HF prognosis⁴¹.

In a recent study, patients homozygous for the Arg16Gln27 haplotype presented a high risk of mortality, whereas those homozygous for the Gly16Glu27 haplotype presented a decrease in this risk. Similar data have been recently published by Shin et al⁴² who verified, in 227 patients with chronic HF treated with beta-blockers, that the individuals homozygous for the Arg16Gln27 haplotype presented a hazard ratio for adverse events (defined by death or heart transplant) of 1.91^{17,42}.

Despite the several studies carried out on the Thr164Ile polymorphism, its role in HF prognosis remains unknown. In a study with 256 patients, Liggett et al analyzed their survival over a one-year period. The Thr164Ile patients had a 42% survival, whereas the Thr164Thr patients presented a survival rate of 76%. However, three subsequent studies could not demonstrate such association^{35,41,43}.

Forleo et al³⁵ analyzed 171 patients with dilated cardiomyopathy and did not find any difference regarding the risk of HF evolution (defined as the need for hospitalization, heart transplant or death) and this polymorphism³⁵.

De Groote et al⁴⁴ analyzed 444 patients with HF and Barbato et al⁴³, 31 patients with HF. These authors did not find an association between the Thr164Ile polymorphism and patients' survival in 3.5 and 2 years, respectively. However, the by Barbato et al demonstrated a faster worsening in HF (increase in diuretics use or the need for hospitalization) in Ile164 patients than in Thr164 ones^{41,44}.

Table 2 summarizes the main effects of the polymorphisms of adrenergic beta-2 receptors on prognosis and response to beta-blockers in HF.

Adrenergic beta-3 receptor polymorphisms

The adrenergic beta-3 receptor gene is located in chromosome 8p11.1-8p12 and it is primarily expressed in white and brown adipose tissue².

The most common polymorphism of this receptor is located in codon 64, where is a substitution of tryptophan by Arginine (Trp64Arg), in the beginning of the first intracellular loop²⁸.

The presence and function of the adrenergic beta-3 in the human heart are still debatable. Some studies have tried, without success, to establish an association between arterial hypertension, coronary disease and this receptor polymorphism. However, the current studies are more directed at the confirmation of the association between the Trp64Arg polymorphism with obesity, insulin resistance and early-stage diabetes mellitus.

Table 2 - Beta-2 adrenergic receptor polymorphisms and their effect on the prognosis and the response to beta-blockers in HF

Polymorphism	Effect	Study
Arg16Gln27	Arg16Gln27: higher risk of death or heart transplant	Kayne et al
Gln27Glu	Gln 27 < Glu 27: response to carvedilol.	Kayne et al
Gln27Glu	Glu > Gln: EF improvement with carvedilol.	Metra et al
Arg16Gly and Gln27Glu	No correlation with HF prognosis.	Liggett et al
Gly16Gln27	Gly16Gln27: lower survival rates.	De Groote et al
Arg16Gln27/ Gly16Glu27	Homozygotes Arg16Gln27 > homozygotes Gly16Glu27: risk of mortality and heart transplant.	Shin et al
Thr164Ile	Thr164Thr > Thr164Ile: better survival.	Liggett et al
Thr164Ile	Thr164 = Ile 164: risk of HF evolution.	Forleo et al
Thr164Ile	Thr164 = Ile 164: survival of 3.5 years.	De Groote et al
Thr164Ile	Ile164 > Thr164: faster HF worsening.	Barbato et al

EF - ejection fraction; HF - heart failure.

Adrenergic alpha-2c receptor and adrenergic beta-1 polymorphisms

The adrenergic alpha-2c receptor is a post-synaptic receptor that prevents the release of noradrenaline at the sympathetic terminal and the deletion of four consecutive amino acids (Del322-325) results in a variant of this receptor that is hypofunctional and is associated to high levels of noradrenaline.

Small et al⁴⁵ demonstrated, in a sample of 84 Black patients, that individuals homozygous for the deletion (322-325) in the alpha-2c receptor gene had a 5-fold higher risk of developing HF when compared to the group that did not have this genotype.

Perspectives

As in genomics, transcriptomics and proteomics, metabolomics is opening new horizons for the more complete analysis of the individual. Metabolomics is considered the link between the genotype and the phenotype. With the global analysis of metabolites, one can have a detailed view of the phenotype, which expedites diagnoses, the development of new pharmacological products and the identification of side effects of new drugs.

In general, it is believed that the use of molecular biology techniques, associated to the conventional morphological and clinical-laboratory criteria will allow a more precise diagnosis and, consequently, a deeper understanding of the physiopathology of cardiac diseases.

The deep knowledge of the process of disease development and the influence of individual factors shall pave the way for a personalized and individual Medicine and for the use of differentiated therapeutic regimens.

Acknowledgements

We would like to thank the GENETIC/UFF project team, especially Professor Georgina Severo Ribeiro for their incentive and untiring work, as well as for the financial support of FAPERJ/DECIT-MS to this molecular genetics project applied to SUS.

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/DECIT.

Study Association

This article is part of the thesis of master submitted by Sabrina Bernardes Pereira, from *Universidade Federal Fluminense*.

References

1. Monçores MW, Pereira SB, Gouvea LSF, Cavalieri BC, Balieiro HM, Tardin OMA, et al. Medicina individualizada aplicada à cardiologia. *Rev SOCERJ*. 2008; 21 (3): 184-93.
2. Atala MM, Consolim-Colombo FM. Influência dos polimorfismos dos genes dos receptores b-adrenérgicos na regulação cardiovascular e no desenvolvimento das doenças cardiovasculares. *Rev Bras Hipertens*. 2007; 14 (4): 258-64.
3. McNamara DM. Emerging role of pharmacogenomics in heart failure. *Curr Opin Cardiol*. 2008; 23 (3): 261-8.
4. Lohse MJ. Beta-adrenoceptor polymorphisms and heart failure. *Trends Mol Med*. 2004; 10: 55-8.
5. Fu C, Wang H, Wang S, Shi Y, Zhou X, Sun K, et al. Association of beta (1)-adrenergic receptor gene polymorphisms with left ventricular hypertrophy in human essential hypertension. *Clin Biochem*. 2008; 41 (10-11): 773-8.
6. Podlowski S, Wenzel K, Luther HP, Müller J, Bramlage P, Baumann G, et al. Beta1-adrenoceptor gene variations: a role in idiopathic dilated cardiomyopathy? *J Mol Med*. 2000; 78 (2): 87-93.
7. Sandilands AJ, O'Shaughnessy KM. The functional significance of genetic variation within the β 1-adrenoceptor. *Br J Clin Pharmacol*. 2005; 60 (3): 235-43.
8. Taylor MR. Pharmacogenetics of the human beta-adrenergic receptors. *Pharmacogenomics J*. 2007; 7 (1): 29-37.
9. Muthumala A, Drenos F, Elliott PM, Humphries SE. Role of β adrenergic receptor polymorphisms in heart failure: systematic review and meta-analysis. *Eur J Heart Fail*. 2008; 10 (1): 3-13.
10. Mason DA, Moore JD, Green SA, Liggett SB. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1- adrenergic receptor. *J Biol Chem*. 1999; 274: 12670-4.
11. Johnson JA, Terra SG. Beta-adrenergic receptor polymorphisms: cardiovascular disease associations and pharmacogenetics. *Pharm Res*. 2002; 19 (12): 1779-87.
12. Rathz DA, Brown KM, Kramer LA, Liggett SB. Amino acid 49 polymorphisms of the human beta(1)-adrenergic receptor affect agonist promoted trafficking. *J Cardiovasc Pharmacol*. 2002; 39: 155-60.
13. Moore JD, Mason DA, Green SA, Hsu J, Liggett SB. Racial differences in the frequencies of cardiac beta(1)-adrenergic receptor polymorphisms: analysis of c145A>G and c1165G>C. *Hum Mutat*. 1999; 14 (3): 271.
14. Rathz DA, Gregory KN, Fang Y, Brown KM, Liggett SB. Hierarchy of polymorphic variation and desensitization permutations relative to beta(1)- and beta(2)-adrenergic receptor signaling. *J Biol Chem*. 2003; 278: 10784-9.
15. Biolo A, Rosa AS, Mazzotti NG, Martins S, Belló-Klein A, Rohde LE, et al. The role of adrenergic receptor polymorphisms in heart failure. *Braz J Med Biol Res*. 2006; 39 (10): 1281-90.
16. Levin MC, Marullo S, Muntaner O, Andersson B, Magnusson Y. The myocardium-protective Gly-49 variant of the beta 1-adrenergic receptor exhibits constitutive activity and increased desensitization and down-regulation. *J Biol Chem*. 2002; 277 (34): 30429-35.
17. Brodde OE. β -1 and β -2 adrenoceptor polymorphisms: functional importance, impact on cardiovascular diseases and drug responses. *Pharmacol Ther*. 2008; 117 (1): 1-29.
18. Wagoner LE, Craft LL, Singh B, Suresh DP, Zengel PW, McGuire N, et al. Polymorphisms of the β 2-adrenergic receptor determine exercise capacity in patients with heart failure. *Circ Res*. 2000; 86: 834-40.
19. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999; 353: 2001-7.
20. Terra SG, Pauly DF, Lee CR, Patterson JH, Adams KF, Schofield RS, et al. β -Adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. *Clin Pharmacol Ther*. 2005; 77: 127-37.
21. Terra SG, Hamilton KK, Pauly DF, Lee CR, Patterson JH, Adams KF, et al. β 1-Adrenergic receptor polymorphisms and left ventricular remodeling changes in response to β -blocker therapy. *Pharmacogenet Genomics*. 2005; 15: 227-34.
22. White HL, de Boer RA, Maqbool A, Greenwood D, van Veldhuisen DJ, Cuthbert R, et al. An evaluation of the beta-1 adrenergic receptor Arg389Gly polymorphism in individuals with heart failure: a MERIT-HF sub-study. *Eur J Heart Fail*. 2003; 5 (4): 463-8.
23. Börjesson M, Magnusson Y, Hjalmarson A, Andersson B. A novel polymorphism in the gene coding for the beta1-adrenergic receptor associated with survival in patients with heart failure. *Eur Heart J*. 2000; 21: 1853-8.
24. Magnusson Y, Levin MC, Eggertsen R, Nyström E, Mobini R, Schaufelberger M, et al. Ser49Gly of β 1-adrenergic receptor is associated with effective β -blocker dose in dilated cardiomyopathy. *Clin Pharmacol Ther*. 2005; 78: 221-31.
25. Small KM, McGraw DW, Liggett SB. Pharmacology and physiology of human adrenergic receptor polymorphisms. *Annu Rev Pharmacol Toxicol*. 2003; 43: 381-411.
26. Taylor MR, Bristow MR. The emerging pharmacogenomics of the beta adrenergic receptors. *Congest Heart Fail*. 2004; 10: 281-8.
27. Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist promoted regulatory properties. *Biochemistry*. 1994; 33: 9414-9.
28. Leineweber K, Büscher R, Bruck H, Brodde OE. Beta-adrenoceptor polymorphisms. *Naunyn Schmiedebergs Arch Pharmacol*. 2004; 369 (1): 1-22.
29. Bruck H, Leineweber K, Buscher R, Ulrich A, Radke J, Insel PA, et al. The Cln27Glu β 2 adrenoceptor polymorphism slows the onset of desensitization of cardiac functional responses in vivo. *Pharmacogenetics*. 2003; 13: 59-66.
30. Bruck H, Leineweber K, Ulrich A, Radke J, Heusch G, Philipp T, et al. The Thr164Ile polymorphism of the human β 2-adrenoceptor exhibits blunted desensitization of cardiac functional responses in vivo. *Am J Physiol Heart Circ Physiol*. 2003; 285: H2034-8.
31. Bruck H, Leineweber K, Park J, Weber M, Heusch G, Philipp T, et al. Human beta2-adrenergic receptor gene haplotypes and venodilation in vivo. *Clin Pharmacol Ther*. 2005; 78: 232-8.
32. Dishy V, Sofowora CG, Xie HG, Kim RB, Byrne DW, Stein CM, et al. The effect of common polymorphisms of the beta2-adrenergic receptor on agonist-mediated vascular desensitization. *N Engl J Med*. 2001; 345: 1030-5.
33. Liggett SB. beta(2)-adrenergic receptor pharmacogenetics. *Am J Respir Crit Care Med*. 2000; 161 (3 Part 2): S197-S201.
34. Heckbert SR, Hindorf LA, Edwards KL, Psaty BM, Lumley T, Siscovick DS, et al. β 2-Adrenergic receptor polymorphism and risk of incident cardiovascular events in the elderly. *Circulation*. 2003; 107: 2021-4.
35. Forleo C, Resta N, Sorrentino S, Guida P, Manghisi A, De Luca V, et al. Association of β -adrenergic receptor polymorphisms and progression of heart failure in patients with idiopathic dilated cardiomyopathy. *Am J Med*. 2004; 117: 451-8.
36. Covolo L, Gelatti U, Metra M, Nodari S, Picciché A, Pezzali N, et al. Role of beta1- and beta2-adrenoceptor polymorphisms in heart failure: a case-control study. *Eur Heart J*. 2004; 25 (17): 1534-41.
37. Liggett SB, Wagoner LE, Craft LL, Hornung RW, Hoit BD, McIntosh TC, et al. The Ile164 β 2-adrenergic receptor polymorphism adversely affects the outcome of congestive heart failure. *J Clin Invest*. 1998; 102: 1534-9.
38. Leineweber K, Tenderich G, Wolf C, Wagner S, Zittermann A, Elter-Schulz M, et al. Is there a role of the Thr164Ile β 2-adrenoceptor polymorphism for the outcome of chronic heart failure? *Basic Res Cardiol*. 2006; 101: 479-84.
39. Kayne DM, Smirk B, Williams C, Jennings G, Esler M, Host D. β -Adrenoceptor genotype influences the response to carvedilol in patients with congestive heart failure. *Pharmacogenetics*. 2003; 13: 379-82.
40. Metra M, Nodari S, Pezzali N, Covolo L,ORIZIO G, Gelatti U, et al. Beta-2 adrenergic receptors polymorphisms influence the effects of carvedilol in the patients with chronic heart failure [abstract]. *Eur J Heart Fail*. 2007; 9 (Suppl 1): 100.
41. De Groot P, Lamblin N, Helbecque N, Mouquet F, McFadden E, Hermant

- X, et al. The impact of beta-adrenoreceptor gene polymorphisms on survival in patients with congestive heart failure. *Eur J Heart Fail.* 2005; 7: 966-73.
42. Shin J, Lobmeyer MT, Gong Y, Zineh I, Langae TY, Yarandi H, et al. Relation of beta(2)-adrenoceptor haplotype to risk of death and heart transplantation in patients with heart failure. *Am J Cardiol.* 2007; 99 (2): 250-5.
43. Barbato E, Penicka M, Delrue L, Van Durme F, De Bruyne B, Goethals M, et al. Thr164Ile polymorphism of β 2-adrenergic receptor negatively modulates cardiac contractility and prognosis in patients with idiopathic dilated cardiomyopathy. *Heart.* 2007; 93: 856-61.
44. De Groote P, Helbecque N, Lamblin N, Hermant X, McFadden E, Foucher-Hossein C, et al. Association between beta-1 and beta-2 adrenergic receptor gene polymorphisms and the response to beta-blockade in patients with stable congestive heart failure. *Pharmacogenet Genomics.* 2005; 15: 137-42.
45. Small KM, Wagoner LE, Levin AM, Kardia SLR, Liggett SB. Synergistic polymorphisms of β 1- and α 2C-adrenergic receptors and the risk of congestive heart failure. *N Engl J Med.* 2002; 347: 1135-42.