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Polymorphism of the Beta-1 Gly389Arg receptor in patients with dual atrioventricular nodal physiology

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ABSTRACT

Introduction: Gly389Arg β1 adrenergic receptor polymorphisms seem to exert an influence on the modulation of the adrenergic effect in several types of patients. This study aimed to determine the prevalence of Gly389Arg polymorphisms among patients with evidence of double nodal pathway and to correlate the electrophysiological properties with the different genotypes of the respective polymorphisms.
Methods: A cross-sectional, descriptive and analytical study was designed to assess 49 patients, with evidence of double nodal pathway, submitted to electrophysiological study. Genomic DNA was extracted from peripheral blood leukocytes and the genotypes of the Arg389Gly polymorphisms were identified in all individuals by PCR/RFLP (polymerase chain reaction/restriction fragment length polymorphism).
Results: The majority of patients were female and had supraventricular tachycardia (75.5%). The prevalence of Arg389Arg genotype was found in 32 patients (65.3%), Arg389Gly genotype in 16 patients (32.7%) and Gly389Gly genotype in 1 patient (2%). With respect to the induction of nodal reentrant tachycardia, it was possible to induce non-isoproterenol tachycardia in 32 patients (65.3%), of whom 24 had the Arg389Arg genotype and 8 the Arg389Gly and Gly389Gly genotype (p = 0.05). The resting heart rate of patients of the Arg389Arg genotype was 81 ± 18 bpm and the Arg389Gly and Gly389Gly genotype of 71 ± 9 bpm (p = 0.044). Body mass index (BMI) among patients with genotype Arg389Gly and Gly389Gly was 29.8 ± 7.1 and patients with the Arg389Arg genotype was 26.2 ± 4.6 (p = 0.034).
Conclusion: The Arg389Arg genotype was more easily related to triggering arrhythmia, higher resting heart rate and lower BMI.

1. Introduction

The knowledge of genetic characteristics associated with cardiovascular disease has attempted to explain part of the heterogeneity observed in the clinical manifestation of the respective diseases. Genetic polymorphisms seem to play an important role as part of this variability. Large-scale genomic association studies have identified areas of the genome in which genes related to cardiovascular disease are likely to be present. Those encoding the beta-adrenergic system are an example of that [1]. There is considerable interindividual and inter-ethnic variability in the response to the adrenergic receptor antagonists [2].

Studies have shown that position 389 of the β1 adrenergic receptor is the one that determines the response to the adrenergic stimulus. Most of the in vitro studies published thus far on β1 adrenergic receptor polymorphisms have shown that Arg389Arg haplotype is associated with a higher degree of adrenergic activation [3,4]. Therefore, it seems logical to assume that the Arg389 haplotype may contribute to a greater degree of adrenergic activation in patients with vascular diseases, which can lead to adverse events such the increased risk of tachyarrhythmia.

Atrioventricular nodal reentry tachycardia (AVNRT) is the most common cause of supraventricular tachycardia (SVT). The classic

mechanistic view of a reentry circuit using two distinct limbs composed of a fast and a slow conducting pathway has being validated by animal and human studies [5]. These pathways have different response to beta-adrenergic stimulation. In our study we assessed the association of the respective β1 adrenergic receptor polymorphisms with the physiological characteristics of the atrioventricular node and AVNRT in patients that required invasive electrophysiological studies (EPS).

2. Materials and methods

2.1. Study setting

We performed a cross-sectional study in patients that were referred for EPS at the Cardiology Institute of Rio Grande do Sul. The aim of the study was to assess the presence of β1 receptor polymorphism and its association with the occurrence of AVNRT and the physiological properties of the atrioventricular node, as well as the arrhythmia per se.

The inclusion criteria were being 18 years of age or more on the date of the EPS, the presence of dual AVN pathways during the EPS and the agreement to participate in the study by providing a signed informed consent form. The exclusion criteria were patients who did not discontinue the use of agents with atrioventricular node blocking action within 4 days and patients with a documented history of structural heart disease.

The clinical data recorded upon admission were gender, age, reason for the indication, weight and height. Patients were brought to the EP laboratory in a post absorptive state where they were monitored by continuous electrocardiogram (ECG) and oxygen saturation. Sedation was performed with fentanyl (25mg bolus) and midazolan (2 mg bolus) or Propofol according to the anesthesiologist. Additional doses were used as needed to increase patient comfort during the procedure. Local anesthesia (lidocaine 2%) was performed in the right groin and three sheaths were advanced into the femoral vein. EP catheters were placed under fluoroscopic view, through the sheaths, in the coronary sinus (decapolar), His bundle region and right ventricle (RV) apex (quadripolars). The data collected during this period were: total dose of sedative drugs used and the Richmond agitation-sedation scale (RASS scale), heart rate before sedation, atrioventricular node refractoriness, Wenckebach cycle length, presence of dual AVN pathways and presence of AVNRT. Isoproterenol was infused in a rate of 1mg/min and increased until the heart rate increased by 20% from its basal state or the arrhythmia induction. For signal recording and programmed stimulation we used a Workmate ® polygraph (St. Jude-US).

The extraction of genomic DNA from whole blood was performed using commercial reagents according to the procedure described by the manufacturer or by the manual method of saline precipitation. Genotypes were detected using the polymerase chain reaction - restriction fragment size polymorphism (PCR-RFLP) [6].

2.2. Statistical analyses

The data was entered into a spreadsheet, using the Excel for Windows program. The analyses performed used the statistical program Statistical Package for Social Sciences (SPSS) 18.0. The frequency of polymorphisms was studied in patients with evidence of double nodal pathway. The comparison of these polymorphisms between patients with and without induction of supraventricular tachycardia was performed using the chi-square test. The electrophysiological variables were compared between the patients with and without the polymorphisms by Student's t-test or chi-square test, where appropriate, and finally, the synergism analysis was performed between the different polymorphisms and their

associations by logistics regression analysis. Categorical variables were expressed as percentage or absolute value and continuous variables were expressed as mean ± standard deviation for those with normal or median distribution and interquartile range for asymmetric variables. Values of $p < 0.05$ were considered to be significant.

2.3. Ethics

The study was designed in accordance with the Directives and Norms Regulating Research Involving Human Beings (Resolution CNS 466/12). The data collected were only used for the study to which they are linked and all the patients signed an Informed Consent Form. The Research Ethics Committee approved the research project.

3. Results

Fifty-five patients were included in the study, and six patients were excluded due to data loss or DNA extraction failure, with 49 patients remaining in the study. Table 1 presents the baseline characteristics of the sample studied.

The mean age of the 49 follow-up patients was 51.3 ± 15.3 years, of which 37 (75.5%) were female patients. The patients analyzed had a tendency to be overweight with a mean Body Mass Index (BMI) of 27.4 ± 5.8. Regarding the indication of the exams, 37 (75.5%) exams were indicated by recorded supraventricular tachycardia. All the exams were performed via the femoral vein and in all the exams 03 venous punctures were performed and 02 diagnostic catheters and 1 ablation catheter were used. In all 49 patients, sedation was used with fentanyl (100%), midazolam was used in 45 (91.8%) patients, and propofol was used in 32 (65.3%) patients, remaining 38 (77.5%) sedated patients on a RASS-1 scale, 8 patients on a RASS-2 scale (16.3%). The mean heart rate before sedation was 77.6 ± 16.2 bpm. The mean Wenckebach period was 361 ± 70.5 ms.

It was necessary to use isoproterenol in 18 (36.7%) patients, and in 45 (91.8%) patients the presence of double nodal route without the presence of isoproterenol was evidenced and 32 (65.3%)

Table 1
Clinical characteristics (n = 49).

Characteristic	(n = 49)
Age, years	51.3 ± 15.3
Female gender, n (%)	37 (75.5)
Body Mass Index (Kg/m^2)	27.4 ± 5.8
Indication, n (%)	
Supraventricular tachycardia	37 (75.5)
Palpitations	9 (18.3)
Syncope	2 (4)
Vascular access, n (%)	
Femoral	49 (100)
Sedation, n (%)	
Fentanyl	49 (100)
Midazolam	45 (91.8)
Propofol	32 (65.3)
Sedation Scale, n (%)	
RASS -1	38 (77.5)
RASS -2	8 (16.3)
RASS 0	3 (6.1)
Use of isoproterenol, n (%)	18 (36.7)
Prevalence of genotype, n (%)	
Arg389Arg	32 (65.3)
Arg389Gly	16 (32.7)
Gly389Gly	1 (2)

Data are expressed as mean ± standard deviation or number (%). RASS: Richmond Agitation-Sedation Scale.

patients were able to trigger nodal reentry tachycardia without the use of isoproterenol. The mean heart rate of nodal reentrant tachycardia without the use of isoproterenol was 179.4 ± 40.6 bpm. The mean ventricular refractory period with a 600 ms basal stimulation cycle was 240.2 ± 40.4 ms. The variables and their relationship to the respective genotypes are shown in Table 2.

Among the patients studied, a prevalence of the Arg389Arg genotype was found in 32 (65.3%), the Arg389Gly genotype in 16 (32.7%) patients and the Gly389Gly genotype in 1 (2%) patient (Fig. 1). The genotype frequencies were in agreement with those predicted by the Hardy−Weinberg equilibrium for the Single Nucleotide Polymorphism (SNP). There was no difference between the genders (p = 0.417) and age in relation to the presence of polymorphism (p = 0.349).

With respect to the induction of nodal reentry tachycardia, it was possible to induce the tachycardia without using isoproterenol in 32 (65.3%) patients, 24 of the Arg389Arg genotype and 8 of the Arg389Gly and Gly389Gly genotype (p = 0.05) (Fig. 2).

Upon assessing the respective variables in this study with respect to the different genotypes, it was found that the resting heart rate of the Arg389Arg genotype patients was 81 ± 18 bpm, while the Arg389Gly and Gly389Gly genotype had 71 ± 9 bpm (p = 0.044).

BMI among patients with the Arg389Gly and Gly389Gly genotype was 29.8 and patients with the Arg389Arg genotype had 26.2 (p = 0.034). The ventricular refractory period with a ventricular pacing cycle of 600 ms in Arg389Arg patients was 237.8 ± 26.3 ms and in patients with the Gly389 allele had 244.7 ± 23.4 ms (p = 0.371).

The Wenckebach period in Arg389Arg patients was 341.2 ± 53.2 ms and among participants with the Gly389 allele was 398.2 ± 84.7 ms (p = 0.0058) (Fig. 3). The presence of a double nodal route without the use of isoproterenol was verified in 45 (91.8%) patients, with no difference between genotypes (p = 0.502). There was no difference regarding the success of ablation between the genotypes (p = 0.568) nor was there between the A-H (p = 0.983) and H−V (p = 0.837) intervals.

4. Discussion

In this study, we demonstrated that the presence of genetic polymorphisms, when assessed jointly, in patients with AVNRT may contribute to identifying patients with a higher propensity to trigger this type of arrhythmia, thus providing useful information for the follow-up and clinical management. To date, few studies have assessed the role of genetic polymorphisms as predictors in triggering cardiac arrhythmias. *Andreasen* et al. have suggested that
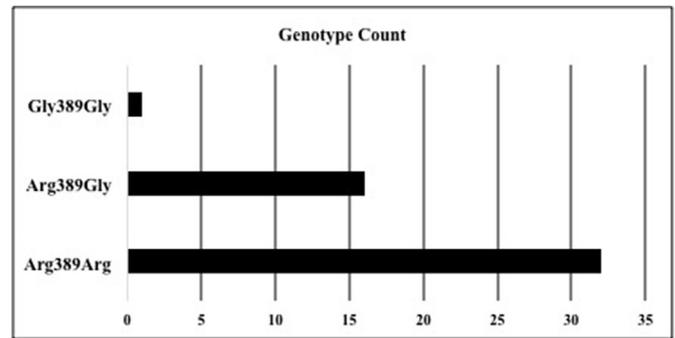

Fig. 1. Prevalence of genotype in patients with evidence of dual atrioventricular nodal pathways.
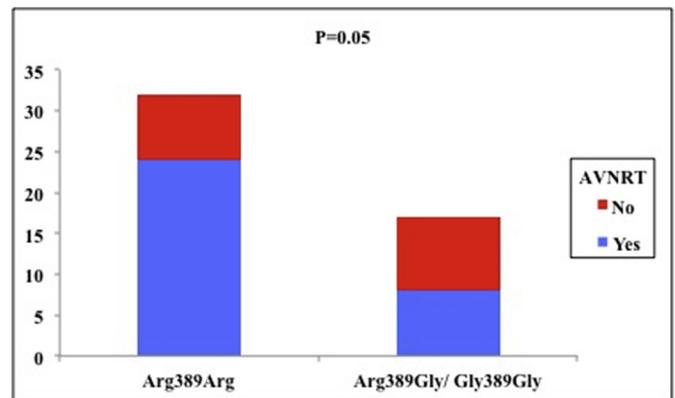Gly389Gly: black. Arg389Gly: black. Arg389Arg: black.

Fig. 2. Relation between induction of tachycardia by nodal reentry and genotypes. AVNRT: atrioventricular nodal reentry tachycardia. No: red. Yes: light blue.

AVNRT might be an electrical arrhythmic disease with abnormal sodium and calcium handling, after performing next generation sequencing of DNA profile of patients and family members with this arrhythmia [7].

Regarding the β1 Arg389Gly gene, this was the first study to assess such a polymorphism in relation to the presence of nodal reentry tachycardia. Our sample consisted mostly of female patients that underwent an electrophysiological study due to supraventricular tachycardia. We observed that patients with the Gly389 allele had greater difficulty in triggering nodal reentry tachycardia, a lower resting heart rate, longer Wenckebach period, and had a higher BMI.

Table 2
Variables and their relationship to genotypes (n = 49).

Variable	Patients (n = 49)	Arg389Arg	Arg389Gly/Gly389Gly	p-value
Age, years	51.3 ± 15.3	49.8 ± 14.9	54.2 ± 16.1	0.349
Female gender, n (%)	37 (75.5)	23 (71.9)	14 (82.4)	0.417
Body Mass Index (Kg/m^2)	27.4 ± 5.8	26.2 ± 4.6	29.8 ± 7.1	0.034
AVNRT	32 (65.3)	24 (75)	8 (47.1)	0.05
Heart rate (bpm)	77.6 ± 16.2	81 ± 18	71 ± 9.0	0.044
Wenckebach periods	361 ± 70.5	341.2 ± 53.2	398.2 ± 84.7	0.005
Ventricular refractory period	240.2 ± 40.4	237.8 ± 26.3	244.7 ± 23.4	0.371
Dual - S	45 (91.8)	30 (93.8)	15 (88.2)	0.502
A-H	83.9 ± 39.6	87.2 ± 46.9	77.8 ± 20.1	0.983
H−V	49.7 ± 8.8	49.5 ± 9.0	50 ± 8.6	0.837
Cardiac ablation	45 (91.8)	29 (90.6)	16 (94.1)	0.568

Data are expressed as mean ± standard deviation or number (%). AVNRT: atrioventricular nodal reentry tachycardia; Dual − S: Dual atrioventricular nodal pathways without use of isoproterenol.
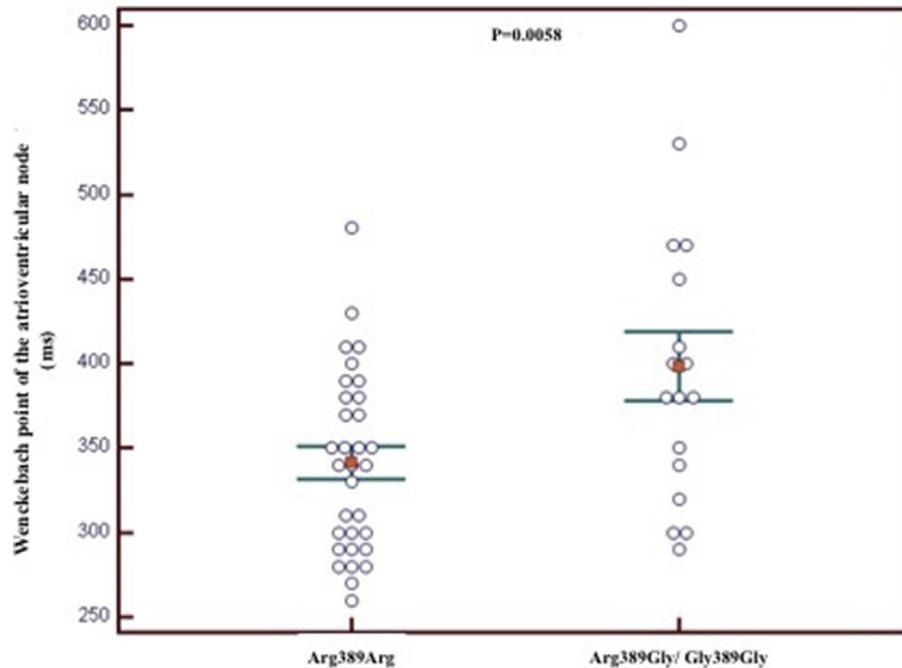A-H: atrium-hissian intervals; H−V: His-Ventricular interval.

Fig. 3. Wenckebach point of the atrioventricular node and relation with the genotypes.
ms: milliseconds. ▮ = Red.

Regarding the greater ease of triggering nodal reentry tachycardia in patients with the Arg389Arg gene, studies point to the protective role that the Gly389 allele provides for arrhythmias, since the Arg389Gly β1 gene causes impaired β1 adrenergic receptor signaling, acting in a similar fashion as beta-blockers and conferring arrhythmogenic protection. As such findings have already been suggested in a previous study in patients with dilated cardiomyopathy [6,8].

Studies have shown a significant association between the Arg389Gly polymorphism and the prevalence of complex ventricular arrhythmias, with a lower prevalence of non-sustained ventricular tachycardia in the presence of the Gly allele [9]. In other studies, the protective factor of the Gly389 allele for atrial fibrillation in the postoperative period of cardiac surgery [10] and the lower prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction were verified [11]. *Nia* et al. demonstrated that both resting heart rate during atrial fibrillation and cardioversion indices were significantly higher in Arg389Arg patients, compared to the other genotypes [12]. In the study by *Iwai* et al., one of the first studies on the subject, in which the sample consisted of 163 patients with idiopathic dilated cardiomyopathy, the Arg389Gly β1-adrenergic receptor polymorphism was significantly related to the presence of ventricular tachycardia when using Holter monitoring, while the Gly389 allele was associated with a lower frequency of ventricular tachycardia [9]. *Chemello* et al., when assessing the β1 Arg389Gly gene in patients with implantable cardioverter-defibrillator and correlating it to the presence of appropriate tachyarrhythmia and therapies, did not observe a statistically significant difference in the incidence of appropriate therapies in the different genotypes [13].

The lower resting heart rate in patients with the Gly389 allele observed in our study could be explained by the fact that the Gly389 allele is a variant of the β1 adrenergic receptor "loss of function," consequently, for the same adrenergic stimulation reduced levels of calcium are produced, thus attenuating the beta-

adrenergic cascade [3]. In the study by *Ranade* et al., it was shown that in patients that are homozygous for the Gly389 allele there was a lower resting heart rate [14]. Regarding the endogenous adrenergic stimulus, in a study with healthy middle-aged individuals that were submitted to exercise, parameters of increased heart rate, blood pressure, contractility and serum renin levels were not different in relation to the haplotypes of the β1 adrenergic receptor Gly389Arg polymorphism [15]. These findings were partially contradicted by *Defoor* et al., who observed the lowest cardiopulmonary VO2 peak in subjects undergoing the effect of exogenous dobutamine [16], while on the other hand, those homozygous for Gly389 had a lower increase in heart rate, myocardial contractility and increased plasma renin levels [17,18]. Although the conflicting results observed in the literature, it's probable that the gain of function role of the Arg389 allele may explain the higher resting heart rates observed in the patients who had this allele in our study. The β-adrenergic variability, which may also be influenced by the Arg389Gly SNP, increases the inward sodium current and accelerates the conduction velocity within the ventricles by changing the sodium channel modes, which might be conductive to the synchronous contraction of the heart [19]. In addition, as modulation is variable, several other uncontrolled factors could also influence the basal heart rate observed in our study.

In our study, the difference observed at the Wenckebach point in patients with the Gly389 allele would probably be related to decreased conduction and increased refractoriness of the atrioventricular node. The activity of L-type calcium channels in the AV nodal N cells determines the velocity of depolarization during the upstroke of an action potential. These calcium channels are further augmented by catecholamine activation of β1-adrenergic receptor mediated channel phosphorylation through enhanced cAMP production. Gly389 is a loss-of-function variant; consequently, for the same adrenergic stimulation, it produces reduced levels of adenyl cyclase and hence attenuates the β-adrenergic cascade and its downstream effect in cardiomyocytes, reducing gain in excitation-

contraction coupling with catecholaminergic surge. Furthermore, the predicted effect of the Arg389Gly variant would be to slow conduction and increase refractoriness in the AV node [14].

The relationship between the Arg389Gly polymorphism and the higher BMI observed in our study can be explained by the role of the β1 adrenergic receptor in energy homeostasis. *Ryden* et al., contrary to the observed results, assessed the relationship between polymorphism and obesity, while failing to demonstrate the higher prevalence of polymorphism in obese patients in their study [20]. However, since the association of BMI and Arg389SNP is speculative, it's possible that our results were incidental. More studies are necessary to confirm this association.

Certain results of the present study may have been influenced by the reduced sample size, which was less than the ideal number for a thorough genetic assessment, which even limited the assessment of the haplotypes. Other limitations of the study that may have influenced the results were the fact that it was conducted at a single center, in a geographically specific area and due to it being a cross-sectional study, it does not allow for the establishment of the cause and effect among the variables.

5. Conclusion

Our data enrich the knowledge on the association between patients with nodal reentry tachycardia and β1-adrenergic receptor genotypes. We observed that patients with the Gly389 allele had greater difficulty in triggering nodal reentry tachycardia, lower resting heart rate, longer Wenckebach period, and had a higher BMI. Although the association does not prove causality, biological plausibility exists in the findings presented.

5.1. Clinical competencies

The current work identifies the prevalence of Gly389Arg polymorphisms among patients with evidence of double nodal pathway and to correlate the electrophysiological properties with the different genotypes of the respective polymorphisms. Findings suggest that the presence of genetic polymorphisms, when assessed jointly, in patients with nodal reentry tachycardia may contribute to identifying patients with a higher propensity to trigger this type of arrhythmia. The genetic analysis and potential recognition of Arg389 allele carriers in patients with AVNRT could potentially identify those individuals with more susceptibility of arrhythmia induction and more able to answer to beta-blockers, thus providing useful information for the follow-up and clinical management.

5.2. Translational outlook

The results of this study should be seen as exploratory and should be used to generate additional hypotheses where additional studies involving other polymorphism risks may add information to genetic parameters and more clearly define the role of genetic polymorphisms in patients with tachyarrhythmia.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Author contributions

D.J.B. and G.G.L. participated in the study design. D.J.B. and G.G.L. performed the statistical analyses. All authors contributed to the interpretation of results, drafted the manuscript and approved the final manuscript.

Declaration of competing interest

The authors report no conflicts of interest.

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