Polymorphisms of the beta-1 and beta-2 adrenergic receptors in Polish patients with idiopathic dilated cardiomyopathy

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Abstract

Background: Dilated cardiomyopathy (DCM) is a disorder characterised by dilation and impaired contractility of the left or both ventricles. This multifactorial disease has a strong genetic component with familial occurrence. A number of genes have been associated with idiopathic DCM (IDCM) including beta-1 (β1-AR) and beta-2 (β2-AR) adrenergic receptors. β1-AR and β2-AR are G-coupled proteins which play an important role in the regulation of heart rate and cardiac contractility. The beta-adrenergic receptor pathway is altered in heart failure. Recent studies have discovered functionally relevant and common polymorphisms in both β1-AR and β2-AR.

Aim: We investigated the frequency of the β1-AR (Ser49Gly, Arg389Gly) and β2-AR (Arg16Gly, Gln27Glu, Thr164Ile) polymorphisms in patients with IDCM in comparison to controls in the Polish population.

Methods: We used a case-control study design comparing a series of consecutive, unrelated 97 IDCM patients with 105 healthy blood donors. Polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP).

Results: There was no significant difference in relation to genotype distribution and allele frequencies of any analysed β1-AR and β2-AR polymorphisms between IDCM patients and controls. The analysis of polymorphism associations did not reveal a higher frequency of coexisting β2-AR Gly16Gln27, Gly16Glu27 and Arg16Gln27 genotypes alone or in combination with the β1-AR Arg389 allele in IDCM.

Conclusion: Our data showed that the studied beta-adrenergic receptor polymorphisms did not seem to play a significant role in IDCM in the Polish population.

Key words: heart failure, idiopathic dilated cardiomyopathy, β1-AR and β2-AR polymorphism

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Introduction

Heart failure (HF) is an important health problem due to its high prevalence and severity of the disease. The prognosis in HF is poor regardless of its aetiology. It may be caused by dilated cardiomyopathy (DCM), a disorder characterised by dilation and impaired contractility of the left or both ventricles [1]. This multifactorial disease has a strong genetic component with familial occurrence in about 25–40% of cases [2]. To date, more than 20 genes responsible for autosomal dominant form of DCM have been described (MIM#115200, [3, 4]). In addition, a number of genes have been associated with idiopathic DCM (IDCM) such as platelet-activating factor (PAF), acetylhydrolase, MHC class II, nebulette, endothelin-A receptor and aldosterone synthase [4]. Also, beta-1 (β1-AR) and beta-2 (β2-AR) adrenergic receptors were related to IDCM [5-7].

Beta-1 and beta-2 adrenergic receptors are G-coupled proteins which play an important role in the regulation of heart rate and cardiac contractility [8]. The beta-adrenergic receptor pathway is altered in HF [9]. Recent studies have discovered functionally relevant and common polymorphisms in both β1-AR (Ser49Gly, Arg389Gly) and β2-AR (Arg16Gly, Gln27Glu, Thr164Ile) genes [10-13].

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The aim of our study was to investigate the frequency of the aforementioned β1-AR and β2-AR polymorphisms in patients with IDCM in comparison to controls in the Polish population.

Methods

Patients

We used a case-control study design comparing a series of consecutive, unrelated 97 IDCM patients. The control group comprised 105 healthy blood donors. All patients and controls belonged to the same European ethnic group. Controls were age-matched with patients; 75% of them were male.

The diagnosis of IDCM was made by left heart catheterisation with a finding of dilated, poorly contracting left ventricle (LV) (LV end-diastolic dimension > 117% of the predicted value corrected for age and body surface area) and LV ejection fraction (LVEF) < 45%, measured angiographically in the absence of any known cause of heart disease. The exclusion criteria included moderate to severe hypertension (> 160/100 mmHg documented on at least two occasions and/or evidence of target-organ disease), a history of hypertension treated with medication, coronary artery disease (obstruction > 50% of the lumen diameter in a major branch), arrhythmogenic right ventricular cardiomyopathy, a history of excessive alcohol consumption, high rate of supraventricular arrhythmia, significant valvular disease, systemic diseases, pericardial disease, congenital heart disease, and cor pulmonale. Familial DCM was diagnosed with at least two subjects within a single family having the diagnosis of DCM confirmed by LV and coronary angiography.

Informed consent was obtained from each patient participating in the study according to the protocol approved by the Local Ethics Committee.

Genotyping

DNA was extracted from fresh blood leukocytes using the phenol-based method [14] or from frozen blood leukocytes using a Nucleo Spin Blood kit (Macherey-Nagel). Polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP). For the Ser49Gly polymorphism, the primers 5'-CCGGGCTTCTGGGGTGTTCC-3' (forward) and 5'- GGCGAGGTGATGGCGAGGTAGC-3' (reverse) were used, as described previously. The 564 bp PCR products were digested by restriction enzyme Eco 0109 I (Fermentas) [15]. For the Arg389Gly polymorphism, the primers 5'-CGCTCTGCTGGCTGCCCTTCTTCC-3' (forward) and 5'-TGGGCTTCGAGTTCACCTGCTATC-3' (reverse) were used. The 530 bp PCR products were digested by restriction enzyme Bcg I (New England Biolabs) [15]. For the Arg16Gly polymorphism previously designed primers 5'-GAACGGCAGCGCCTTCTTGCTGGCACCCCAT-3' (forward) and 5'-CTGCCAGGCCCATGACCAGATCAG-3' (reverse)] were used. The 242 bp PCR products were digested by restriction enzyme Eco 130I (Fermentas) [16]. For the Gln27Glu polymorphism, the primer pair was the same as for the Arg16Gly polymorphism. PCR products were digested by restriction enzyme Sat I (Fermentas) [16]. For the Thr164Ile polymorphism, the primers 5'-GTGATCGCAGTGGATCGCTACT-3' (forward) and 5'-AGACGAAGACCATGATCACCAG-3' (reverse) 280 bp PCR products were digested by restriction enzyme Mnl I (Fermentas) as described previously [16]. The digestion of PCR products was followed by an analysis by 2% agarose gel electrophoresis (Sigma) and visualisation by means of ethidium bromide staining.

Statistical analysis

Continuous variables are presented as means and standard deviations for normal distribution or median and interquartile range for skewed variables. Categorical data are presented as frequencies. The differences in clinical variables, in the distribution of β1-AR and β2-AR genotypes and allele frequencies were assessed using the unpaired t-test, chi square and Fisher's exact tests. To test for Hardy-Weinberg equilibrium for each polymorphism, the expected genotype numbers were calculated from the allele frequencies and the deviation from the observed genotype numbers was determined using the chi square test. In order to test for the effect of each genotype and their interactions the odds ratio (OR) and 95% confidence intervals (CI) for IDCM and controls were computed. Statistical analysis was performed with SAS software version 9e (SAS Institute Inc., Cary, NY). A value of $p < 0.05$ was considered significant.

Results

Baseline clinical and haemodynamic characteristics of the studied IDCM patients are shown in Table I. Studied polymorphisms were in Hardy-Weinberg equilibrium when comparing the expected and actual genotype frequencies in all groups. There were no significant differences in terms of analysed genotypes or alleles between affected and control individuals (Tables II and III). Beta 1-AR Gly49Gly genotypes did not occur among IDCM patients, while β2-AR Ile164Ile did not occur among any of the groups.

Since Gly49 homozygosis was uncommon in our population, and Ile164 homozygosis was absent, we went on to analyse only β1-AR Arg389Gly, β2-AR Arg16Gly and β2-AR Gln27Glu polymorphisms. Three risk haplotypes of combined B2-AR polymorphism remaining in linkage disequilibrium [17], Gly16Gln27, Gly16Glu27, and Arg16Gln27, were chosen according to the published clinical data on increased β2-AR downregulation in their carriers [10, 11]. The association analysis showed no significant differences in their distribution in patients and controls (Table IV).

Finally, we investigated the distribution of the above β2-AR risk haplotypes in combination with the Arg allele of β1-AR Arg389Gly polymorphism, previously related to increased receptor sensitivity [12]. The analysed haplotypes were as follows: Arg389Gly16Gln27, Arg389Gly16Glu27, Arg389Arg16Gln27. There was no difference in the distribution of the haplotypes studied between controls and IDCM patients (Table V).

Discussion

We demonstrated that there was no significant association between β1-AR Ser49Gly, Arg389Gly or β2-AR Arg16Gly, Gln27Glu and Thr164Ile polymorphisms and IDCM in the Polish population. There was also no relationship between previously described combined β2-AR risk haplotypes alone or in association with β1-AR Arg339 risk allele and IDCM.

An *in vitro* study demonstrated that the Arg16 allele of the β2-AR Arg16Gly polymorphism and the Glu27 allele of the β2-AR Gln27Glu polymorphism were linked to resistance to agonist-promoted downregulation of the β1-AR receptor [10, 11].

A previously published clinical study showed that both of those alleles might be related to a lower risk of IDCM and sudden death [6]. Shin et al. also demonstrated an association between β2-AR Arg16Arg Glu27Gln haplotype and an increased risk of death or heart transplantation due to HF [18]. On the other hand, Covolo et al. described no association between those alleles and HF [19].

It has already been shown that linkage disequilibrium occurred between the β2-AR Arg16Gly and Gln27Glu polymorphisms [17]. Our study confirmed that all patients homozygous for the Glu27 allele were also homozygous for the Gly16 allele.

Table I. Demographic and clinical characteristics of patients with IDCM

Variable	n = 97
Age [years]	38.84 ± 13.46
Male sex [%]	86
Familial disease [%]	18
Duration of symptoms [months]	24.62 ± 37.40
NYHA class I/II [%]	41
NYHA class III/IV [%]	60
Sinus rhythm [%]	74
LVEDD [mm]	69.78 ± 9.10
FS [%]	17.50 ± 5.34
LVEF [%]	28 ± 11.5
PCWP [mmHg]	19.11 ± 10.00
PASP [mmHg]	37.79 ± 16.31
CI [l/min/m^2]	2.51 ± 0.91
Beta-blocker treatment [%]	88

Abbreviations: NYHA – New York Heart Association, LVEDD – left ventricular end diastolic dimension, FS – fractional shortening, LVEF – left ventricular ejection fraction, PCWP – mean pulmonary capillary wedge pressure, PASP – pulmonary artery systolic pressure, CI – cardiac index

We demonstrated that the β2-AR Ile164 allele is very rare in the Polish population. In accordance with another HF study [20], we found no differences in the allele frequencies and genotype distribution between the groups studied. However, an in vitro study showed that the Ile164 protein displayed a lower binding affinity for epinephrine as compared with the wild type receptor [11]. The Ile164 receptor displayed greater desensitisation than the wild type receptor [13].

Table II. Frequency and odds ratios (OR) for IDCM according to beta-1 receptor genotypes

Genotypes	IDCM	Controls	OR (95% CI), p
	n (%)	n (%)	
β1-AR (codon 49)			
Ser/Ser	76 (78.0)	87 (83.0)	reference
Ser/Gly	21 (22.0)	17 (16.0)	1.4 (0.7-2.9), p = 0.37
Gly/Gly	0 (0.0)	1 (1.0)	
Allele frequency			
Ser	(91.0)	(89.0)	
Gly	(9.0)	(11.0)	
β1-AR (codon 389)			
Arg/Arg	57 (59.0)	50 (48.0)	reference
Arg/Gly	35 (36.0)	47 (45.0)	0.7 (0.4-1.1), p = 0.19
Gly/Gly	5 (5.0)	8 (7.0)	0.5 (0.2-1.8), p = 0.38
Allele frequency			
Arg	(77.0)	(70.0)	
Gly	(23.0)	(30.0)	

Table III. Frequency and odds ratios (OR) for IDCM according to beta-2 receptor genotypes

Genotypes	IDCM		Controls		OR (95% CI), p
	n	(%)	n	(%)	
β2-AR (codon 16)					
Arg/Arg	15	(15.0)	14	(13.0)	reference
Arg/Gly	47	(49.0)	46	(44.0)	1.0 (0.4-2.2), p = 1
Gly/Gly	35	(36.0)	45	(43.0)	0.7 (0.3-1.7), p = 0.51
Allele frequency					
Arg		(40.0)		(35.0)	
Gly		(60.0)		(65.0)	
β2-AR (codon 27)					
Gln/Gln	23	(25.0)	33	(31.0)	reference
Gln/Glu	56	(57.0)	51	(49.0)	1.6 (0.8-3.0), p = 0.19
Glu/Glu	18	(18.0)	21	(20.0)	1.2 (0.5-2.8), p = 0.68
Allele frequency					
Gln		(53.0)		(56.0)	
Glu		(47.0)		(44.0)	
β2-AR (codon 164)					
Thr/Thr	94	(97.0)	103	(98.0)	reference
Thr/Ile	3	(3.0)	2	(2.0)	1.6 (0.3-10.1), p = 0.67
Allele frequency					
Thr		(98.0)		(99.0)	
Ile		(2.0)		(1.0)	

Ile164Ile vs. Thr/Thr not available, because the genotype did not occur

Table IV. Odds ratios for IDCM according to allele combinations of β2-AR genes

β2-AR genotypes	IDCM		Controls		OR (95% CI), p
	n	(%)	n	(%)	
Arg16*Glu27* + Gly16Glu27* + Arg16*Gln27	94	(96.9)	101	(96.2)	reference
Gly16Gln27#	3	(3.1)	4	(3.8)	0.8 (0.2-3.7), p = 1
Arg16*Gln27* + Gly16Gln27* + Arg16*Glu27	79	(81.4)	78	(74.3)	reference
Gly16Glu27#	18	(18.6)	27	(25.7)	0.7 (0.3-1.3), p = 0.24
Gly16*Glu27* + Arg16Glu27* + Gly16*Gln27	82	(84.5)	90	(85.7)	reference
Arg16Gln27#	15	(15.5)	15	(14.3)	1.1 (0.5-2.4), p = 0.84

** allele in homozygous or heterozygous state*
 # risk genotype

Our results regarding β1-AR Ser49Gly polymorphism are in agreement with another study where there was no difference in allele frequencies between HF patients and healthy controls [21], but they differ from the results reported by other groups where the Gly49 allele was associated with a higher risk of IDCM [6,22].

Results concerning β1-AR Arg389Gly polymorphism are various. Tesson et al. showed no differences in Arg389Gly distribution between IDCM patients and healthy controls [5]. A few other studies found no association between HF and Arg389Gly genotypes [19, 23], while another study discovered increased frequencies of the Gly389 allele in IDCM patients [7]. The result reported by Small et al. showed that among African-American patients, combined homozygosity for α_{2c}Del322-325 and β1-AR Arg389Gly was associated with the risk of HF [24]. On the other hand, α_{2c}Del322-325 β1-AR Arg389Gly genotypes were not associated with measures of LV structure and function [25]. The Arg389 receptor displays increased coupling to Gs and stimulation of adenylyl cyclase as compared with the Gly variant [12]. Genotyped human ventricles from β1-AR Arg389 carriers show a greater agonist promoted contractility versus Gly389 carriers [26]. In addition, the β1-AR Arg389Gly

Table V. Odds ratios for IDCM according to allele combinations of β1- and β2-AR genes

β1- and β2-AR genotype combinations	IDCM n (%)	Controls n (%)	OR (95% CI), p
Gly389*Arg16*Glu27*/Gly389*Arg16*Gln27/ Gly389*Gly16Glu27*/Gly389*Gly16Gln27/ Arg389Arg16*Glu27*/Arg389Arg16*Gln27/ Arg389Gly16Glu27*	96 (99.0)	103 (98.1)	reference
Arg389Gly16Gln27#	1 (1.0)	2 (1.9)	0.5 (0.1-6.0), p = 1
Gly389*Arg16*Glu27*/Gly389*Gly16Gln27*/ Gly389*Arg16*Glu27/Gly389*Gly16Gln27/ Arg389Arg16*Gln27*/Arg389Gly16Gln27*/ Arg389Gly16*Glu27*	89 (91.8)	93 (88.6)	reference
Arg389Gly16Glu27#	8 (8.2)	12 (11.4)	0.7 (0.3-1.8), p = 0.49
Gly389*Gly16*Glu27*/Gly389*Arg16Glu27*/ Gly389*Gly16*Gln27/Gly389*arg16Gln27/ Arg389Gly16*Glu27*/Arg389Arg16Glu27*/ Arg389Gly16*Gln27	89 (91.8)	101 (96.2)	reference
Arg389Arg16Gln27#	8 (8.2)	4 (3.8)	2.3 (0.7-7.8), p = 0.24

** allele in homozygous or heterozygous state*
 # risk genotype combination

polymorphism affects the beta-blocker therapeutic response in HF [26].

It has been shown that the combination of the Arg389 allele, associated with increased sensitivity to β1-AR agonist, and the β2-AR Gly16glu27 haplotype, when linked to the increased agonist-promoted downregulation of the receptor, could be preferentially associated with IDCM [10]. Our study revealed no such preferential association in IDCM patients compared with controls. These results are in agreement with another study where there was no difference in the aforementioned haplotype frequencies between HF patients and healthy controls [19].

A limitation of our study was the relatively small number of patients included. Further investigations on a larger population are needed. The analysis of haplotypes and allele combinations may show a significant association in larger study groups.

To sum up, our data showed that β1-AR Ser49Gly, Arg389Gly or β2-AK Arg16Gly, Gln27Glu and Thr164Ile polymorphisms alone or in combination do not play a significant role in IDCM in the Polish population.

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Polimorfizm receptorów adrenergicznych beta-1 i beta-2 u polskich pacjentów z idiopatyczną kardiomiopatią rozstrzeniową

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Streszczenie

Wstęp: Niewydolność serca jest poważnym problemem zdrowotnym z powodu ciężkości przebiegu i dużej śmiertelności. Niewydolność serca, a w szczególności kardiomiopatia rozstrzeniowa (ang. *dilated cardiomiopathy*, DCM), jest chorobą o złym rokowaniu. Choroba ta charakteryzuje się rozstrzenią i upośledzoną kurczliwością lewej albo obydwóch komór. Ta wieloczynnikowa choroba ma ważny komponent genetyczny występujący w postaci rodzinnej (25–40%). Do tej pory opisano ponad 20 genów odpowiedzialnych za wystąpienie autosomalnej dominującej formy DCM (MIM#115200) oraz liczne geny skorelowane z idiopatyczną formą DCM (ang. *idiopathic dilated cardiomiopathy*, IDCM), kodujące takie białka, jak: płytkowy czynnik aktywujący (PAF), acetylohydrolaza, MHC klasy II, receptor endoteliny czy syntaza aldosteronu. Polimorfizmy receptorów adrenergicznych beta-1 i beta-2 (β1-AR i β2-AR) także zostały opisane jako czynniki mające wpływ na wystąpienie i przebieg IDCM. Receptory β1-AR i β2-AR są połączone funkcjonalnie z białkiem G, które odgrywa ważną rolę w regulacji pracy serca. Szlaki β1-AR i β2-AR ulegają zmianie w przebiegu IDCM. Ostatnio pojawiło się kilka prac opisujących wpływ polimorfizmów występujących w genach kodujących β1-AR i β2-AR, w szczególności Ser49Gly, Arg389Gly w β1-AR oraz Arg16Gly, Gln27Glu, Thr164Ile w β2-AR.

Cel: Zbadanie częstości występowania ww. polimorfizmów u chorych z IDCM w porównaniu z grupą kontrolną w polskiej populacji.

Metody: Badania przeprowadzono w grupie niespokrewnionych chorych z IDCM (97 osób) w porównaniu z grupą kontrolną, którą stanowili zdrowi dawcy krwi (105 osób). Polimorfizmy genów kodujących β1-AR: Gly49Gly, Arg389Gly, i β2-AR: Arg16Gly, Gln27Glu, Thr164Ile, określono metodą RFLP (*restriction fragment length polymorphisms*).

Wyniki: Nie znaleziono żadnych statystycznie istotnych różnic w dystrybucji poszczególnych genotypów ani w częstości występowania poszczególnych alleli analizowanych polimorfizmów między grupą badaną a kontrolną. Analiza sprzężeń poszczególnych polimorfizmów nie wykazała zwiększonej częstości występowania genotypów β2-AR: Gly16Gln27, Gly16Glu27 i Arg16Gln27, osobno lub w kombinacji z allelami β1-AR: Arg389, u chorych z IDCM.

Wnioski: Nasze dane pokazały, że badane polimorfizmy receptorów beta-adrenergicznych nie odgrywają istotnej roli u chorych z IDCM w polskiej populacji.

Słowa kluczowe: niewydolność serca, idiopatyczna kardiomiopatia rozstrzeniowa, polimorfizm β1-AR i β2-AR

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