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Effect of *ADRB1* 1165C>G and 145A>G polymorphisms on hemodynamic response during dobutamine stress echocardiography

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Abstract

Purpose The aim of the study was to determine an association between *ADRB1* 1165C>G and 145A>G polymorphisms and heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure response to dobutamine during dobutamine stress echocardiography (DSE).

Methods The study involved 144 patients with clinical indications for DSE. PCR-RFLP method was used to identify *ADRB1* 1165C>G and 145A>G polymorphisms.

Results HR during DSE increased in all analyzed groups of the study. Patients in *ADRB1* 1165CC and 1165CG+GG demonstrated similar HR, including magnitude of response (Δ HR 0-30) – 42.1 ± 17.5 bpm vs. 46.1 ± 15.5 bpm, respectively. Likewise, HR and Δ HR 0-30 were comparable in *ADRB1*145AA and 145AG subjects in the course of DSE. SBP and DBP at all stages of DSE were similar within both polymorphisms analyzed, and did not differentiate *ADRB1*145AA from 145AG subjects as well as *ADRB1* 1165CC from 1165CG+GG cases. Similarly any differences were noted in the magnitude of response, the increase in SBP and DBP were comparable in all genotypes. Similar observations were made in patients (25 out of 144 studied) with atropine requirements during DSE.

Conclusion The *ADRB1* 1165C>G and 145A>G polymorphisms are not associated with HR, SBP and DBP response in Polish Caucasian patients subjected for diagnostic dobutamine stress echocardiography

Keywords *ADRB1*, 1165C>G and 145A>G polymorphism, dobutamine stress echocardiography

Introduction

The regulation of cardiovascular response, i.e. heart rate (HR) and blood pressure both systolic (SBP) and diastolic (DBP) during physical stress is controlled by environmental and genetic factors. Available data demonstrated association of several genes, which might influence response rate measured by aforementioned parameters, namely encoding beta1-adrenergic receptor [1,2], G-protein alpha subunit [3,4], G-protein beta3 subunit [5].

Beta-adrenoreceptor system plays an important role in the regulation of human cardiovascular system. Within beta1-adrenergic receptor gene two common polymorphisms were defined: *ADRB1* Arg389Gly (rs1801253, c.1165C>G in exon 1 and Ser49Gly (rs1801252, c.145A>G in exon 1). In vitro studies have provided evidence for their functional basis, and these polymorphisms have been implicated in differential response to β_1 -agonists and antagonists in numerous studies [6-10]. However, only few data referred to effects of *ADRB1* polymorphisms on heart function in stress situations, and the reported data are contradictory, from a significant associations to a complete lack of influence [12-14].

Dobutamine is an inotropic synthetic catecholamine commonly used as a diagnostic tool for dobutamine stress echocardiography (DSE). Due to dobutamine positive inotropic and chronotropic effects DSE has become a popular method for evaluation of coronary artery disease in patients unable to undergo standard exercise stress tests. However, clinical observations demonstrate interpersonal variations in response to dobutamine or exercise test as for heart rate (with some patients requiring atropine administration due to inability to complete the test and achieve target HR) and blood pressure response [11,12,13]. Polymorphisms within genes involved in regulation of the heart function might shed light on the observed diversity in heart response to dobutamine. One of potential candidate is the *ADRB1* gene.

The aim of this study was to determine an association between *ADRB1* gene polymorphisms with heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) response to dobutamine during DSE.

Methods

Subjects

One hundred forty four subjects of Caucasian origin (77 women and 67 men, aged 31-80) with clinical indication for DSE were enrolled in the study. Of them 25 patients required atropine administration during DSE. DSE was indicated for detection of coronary artery disease in subjects who were unable to undergo standard exercise stress testing. Detailed

characteristics of patients recruited for the study is presented in table 1. The study protocol was approved by local ethics committee (Pomeranian Medical University, Szczecin, Poland), and all study participants gave informed written consent.

Clinical assay

Dobutamine stress echocardiography was performed according to standard guidelines using escalating administration of dobutamine (from 10, 20, 30 to 40 $\mu\text{g}/\text{kg}/\text{min}$ with a 3-minute interval) [15]. HR (based on 12-lead electrocardiogram) and blood pressure were measured at baseline (after a rest period), at the start of the dobutamine infusion period and at the end of each 3-min. In patients with atropine requirements, i.e. in subjects who were not able to reach target HR at dobutamine dose of 30 $\mu\text{g}/\text{kg}/\text{min}$, the drug was administered in divided doses beginning from 0.25mg up to 1.0 mg. Most patients subjected for evaluation reached target HR at dobutamine level 30 $\mu\text{g}/\text{kg}/\text{min}$, which was than the end time point for analysis. Each subject discontinued β -blockers and/or calcium channel blockers five half-lives of the drug before the study onset.

Genotyping

Genomic DNA was extracted from samples of peripheral blood leukocytes according to a standard protocol. Genotyping of *ADRB1* Arg389Gly (rs1801253, c.1165C>G in exon 1 and Ser49Gly (rs1801252, c.145A>G in exon 1) polymorphisms, based on PCR-RFLP method with *BsmFI* and *Eco0109I* restriction enzymes, respectively, was performed as described previously [16].

Statistical analysis

Based on allele frequencies, it was expected that the number of *ADRB1* 1165GG and 145GG homozygotes would be low. As such, it was planned a priori that *ADRB1* 1165GG and 145GG homozygotes would be combined with heterozygotes. Conformity of genotype distributions to Hardy-Weinberg law was assessed using χ^2 -test. Categorical baseline characteristics were compared between groups using the Fisher exact test (Statistica 8.0, Statsoft Software, Warsaw, Poland). Numerical variables between groups were evaluated by U Mann-Whitney test. A *p* level of less than 0.05 was considered statistically significant.

Results

Both groups of the study, i.e. subjects stratified according to *ADRB1* 1165C>G and 145A>G polymorphisms did not differ significantly in any of the parameters presented in table 1 (which contains general data), i.e. by age, sex, BMI, smoking habits, coexistent cardiovascular diseases and medication. Genotype and allele distributions fitted Hardy-Weinberg equilibrium in both study groups. Taking into account the observed genotype frequencies and SD, our study in 119 patients has over 80% power to detect differences in SBP, DBP and HR if they exceed 9.5; 5.8; 6.4 in case of Ser49Gly and 8.5; 5.0; 5.5 in case of Arg389Gly polymorphism. As for differences between starting parameters and observed after application of 30 µg of dobutamine, our study exceeds 80% power when the difference of mean values between genotype-stratified patients would be greater than 11.6 (ΔSPB), 4.9 (ΔDBP) and 10.4 (ΔHR) for Ser49Gly polymorphism and 10.0; 4.3; 9.1 in case of Arg389Gly polymorphism.

Resting Haemodynamics

All resting haemodynamic parameters were similar in *ADRB1* 1165C>G and 145A>G carriers. Patients with *ADRB1* 1165CC and 1165CG+GG as well as 145AA and 145AG genotypes were characterized by comparable resting HR, SBP and DBP (Table 2).

HR, SBP and DBP response during DSE

HR during DSE increased in all analyzed groups of the study. Patients in *ADRB1* 1165CC and 1165CG+GG demonstrated similar HR, including magnitude of response (ΔHR 0-30) – 42.1±17.5 bpm vs. 46.1±15.5 bpm, respectively. Likewise, HR in the course of DSE and ΔHR 0-30 were comparable in *ADRB1*145AA and 145AG subjects (Table 3).

SBP at all stages of DSE was similar within both polymorphisms analyzed, and did not differentiate *ADRB1*145AA from 145AG subjects as well as *ADRB1* 1165CC from 1165CG+GG cases. Similarly any differences were noted in magnitude of response (Table 4).

DBP response in the course of DSE was similar in both analyzed polymorphisms of *ADRB1* gene. DBP decreased during DSE at a rate comparable in all analyzed *ADRB1* subgroups. Similar trend was observed for magnitude of DBP response (Table 5).

Similarly to patients not requiring atropine, subjects with atropine demands were characterized by similar HR, SBP, DBP and magnitude of hemodynamic response in all analysed groups of *ADRB1* polymorphisms (except for some isolated SBP measurements) (Table 6).

Discussion

The study was dedicated to define the role of *ADRB1* 1165C>G and 145A>G polymorphisms in interindividual variability to dobutamine response during DSE (among patients with clinical indication for the test). Available data are not consistent as for associations of *ADRB1* SNPs with hemodynamic response during stress situations, including DSE. The present study did not demonstrate significant association between *ADRB1* 1165C>G and 145A>G polymorphisms and parameters of hemodynamic response during DSE, i.e. with HR, SBP, DBP and magnitude of response within the aforementioned parameters, both in patients with and without atropine requirements within standard DSE protocol. Our observation is in keeping with the data reported by Aquilante et al. [2]. The authors did not show any influence of *ADRB1* 1165C>G and 145A>G polymorphisms on HR, SBP and DBP response in American Caucasians during DSE, which was clinically indicated (with four half-lives beta-adrenolytics withdrawal before the study onset). Similar observations were also reported by Kindermann et al. [17], who studied the effect of dobutamine administered in DSE protocol on HR, SBP and contractility parameters. The authors did not note any association between *ADRB1* 1165C>G and 145A>G polymorphisms and HR and SBP. The *ADRB1* 1165C>G polymorphism was associated with other hemodynamic parameters (systemic vascular resistance, ventricular end-systolic meridional wall stress). The *ADRB1* 145A>G polymorphism had no effect on any of the measured parameters. Our study and the reports of Aquilante et al. [2] as well as Kindermann et al. [17] are in contrast to German data presented by La Rosee et al. [14]. The latter authors evaluated influence of *ADRB1* 1165C>G polymorphism on hemodynamic response in healthy volunteers premedicated with atropine in order to block parasympathetic system. They found significant association between the *ADRB1* polymorphism and SBP, where *ADRB1* 1165CC homozygotes had a greater increase in SBP response to dobutamine during DSE than 1165GG cases. The differences between our and Aquilante et al. [2] findings and these of La Rosee et al. [14] might be attributed to different populations studied, i.e. our and the Aquilante et al. [2] cohorts were recruited among patients with clinical indication for DSE, opposite to healthy volunteers analyzed by La Rosee et al. [14]. However, negative results reported by Kindermann et al. [17] were also from healthy population. Another factor which should be considered is parasympathetic system blockade produced by La Rosee et al. [14] with atropine administration, which might attenuate genotype related response to dobutamine in patients from our and Aquillante et al. [2] studies. La Rosee et al. administered atropine to healthy volunteers prior to the study, and observed effects of *ADRB1* polymorphism under cholinergic blockade, whereas from our

study it can be concluded that patients demanding atropine to complete DSE were not stratified according *ADRB1* polymorphisms. HR was also not associated with *ADRB1* 1165C>G and 145A>G polymorphisms in Finnish study conducted in patients subjected to exercise test from clinical indications. In the latter study, an association was noted between *ADRB1* 1165C>G maximal SBP during exercise and SBP changes from rest to maximal [13]. Summary of conducted studies with respect to association of hemodynamic changes during stress with *ADRB1* polymorphism is presented in table 7.

The parameter which was not affected by *ADRB1* 1165C>G polymorphism in the three cited above studies was HR during DSE. All studies provided evidence that the *ADRB1* polymorphism is not associated with HR response during DSE.

In summary, the *ADRB1* 1165C>G and 145A>G polymorphisms are not associated with HR, SBP and DBP response in Polish Caucasian patients subjected for diagnostic dobutamine stress echocardiography.

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Table 1 Patient characteristics

Parameter	mean±SD or n(%)
Age (years)	59.3 ± 8.8
Sex	
females	65 (54.62 %)
males	54 (45.38 %)
BMI (kg/m ²)	27.8 ± 3.85
Smoking	19 (15.97 %)
Hypertension	78 (65.55 %)
Diabetes	15 (12.60 %)
Medication	
1. ACE	55 (46.22 %)
2. ASA	72 (60.50 %)
3. b-blockers	68 (57.14 %)
4. Ca ²⁺ -blockers	23 (19.33 %)
5. Statins	68 (57.14 %)
6. Diuretics	28 (23.53 %)

Table 2 Resting systolic blood pressure (SBP), diastolic (DBP) and heart rate (HR) (mean±SD)

<i>ADRB1</i>	genotype	mean SBP (mmHg)	p	mean DBP (mmHg)	p	mean heart rate HR (bpm)	p
145A>G	AA (n=90)	133,4 ± 15,7	0,948	83,4 ± 9,8	0,655	70,5 ± 10,7	0,104
	AG (n=29)	133,6 ± 16,4		82,8 ± 8,4		66,9 ± 9,8	
1165C>G	CC (n=67)	132,4 ± 15,2	0,516	83,3 ± 9,3	0,719	69,3 ± 10,1	0,800
	GC+GG (n=52)	134,7 ± 16,7		83,3 ± 9,8		70,0 ± 11,2	

U Mann-Whitney test

Table 3 Heart rate (HR, bpm) and increase in heart rate (Δ HR) at consecutive stages of DSE (mean±SD)

Dobutamine dose (μ g/kg/min)	<i>ADRB1</i> 145A>G		p	<i>ADRB1</i> 1165C>G		p
	AA (n=90)	AG (n=29)		CC (n=67)	GC+GG (n=52)	
HR 0	70.5 ± 10.7	66.9 ± 9.8	0.104	69.3 ± 10.1	70.0 ± 11.2	0.800
HR 10	75.7 ± 10.6	71.7 ± 9.2	0.079	74.8 ± 10.3	74.7 ± 10.6	0.735
HR 20	92.7 ± 17.3	89.3 ± 10.5	0.347	92.9 ± 19.5	90.5 ± 16.2	0.456
HR 30	112.6 ± 19.9	113.0 ± 18.3	0.988	114.5 ± 19.4	110.5 ± 19.5	0.286
Δ HR 0-30	42.1 ± 17.5	46.1 ± 15.5	0.211	45.1 ± 18.1	40.5 ± 15.4	0.193

U Mann-Whitney test

Table 4 Systolic blood pressure (SBP, mmHg) and its increase (Δ SBP) at consecutive stages of DSE (mean \pm SD)

Dobutamine dose (μ g/kg/min)	ADRB1145A>G		p	ADRB11165C>G		p
	AA (n=90)	AG (n=29)		CC (n=67)	GC+GG (n=52)	
SBP 0	133.4 \pm 15.7	133.6 \pm 16.4	0.948	132.4 \pm 15.2	134.7 \pm 16.7	0.516
SBP 10	138.5 \pm 16.0	138.2 \pm 16.9	0.988	137.7 \pm 16.2	139.3 \pm 16.3	0.679
SBP 20	146.7 \pm 19.4	147.6 \pm 21.7	0.861	146.2 \pm 20.0	147.8 \pm 19.9	0.796
SBP 30	150.5 \pm 20.2	150.9 \pm 27.2	0.948	149.6 \pm 22.2	151.9 \pm 21.9	0.530
Δ SBP 0-30	17.1 \pm 16.9	17.3 \pm 25.1	0.719	17.1 \pm 20.6	17.2 \pm 17.2	0.755

U Mann-Whitney test

Table 5 Diastolic blood pressure (DBP, mmHg) and its increase (Δ DBP) at consecutive stages of DSE (mean \pm SD)

Dobutamine dose (μ g/kg/min)	ADRB1145A>G		p	ADRB11165C>G		p
	AA (n=90)	AG (n=29)		CC (n=67)	GC+GG (n=52)	
DBP 0	83.4 \pm 9.8	82.8 \pm 8.4	0.655	83.3 \pm 9.3	83.3 \pm 9.8	0.719
DBP 10	87.6 \pm 10.5	83.5 \pm 13.7	0.181	87.0 \pm 11.6	86.2 \pm 11.3	0.900
DBP 20	84.0 \pm 9.5	82.7 \pm 9.5	0.319	83.3 \pm 10.4	84.3 \pm 8.1	0.573
DBP 30	80.8 \pm 9.0	79.9 \pm 11.2	0.719	80.1 \pm 10.6	81.3 \pm 8.1	0.443
Δ DBP 0-30	-2.6 \pm 7.9	-2.9 \pm 8.9	0.890	-3.2 \pm 7.9	-1.9 \pm 8.4	0.664

U Mann-Whitney test

Table 6 Heart rate (HR, bpm), SBP (mmHg) DBP (mmHg) and increase in heart rate (Δ HR), SBP (Δ SBP), DBP (Δ DBP) at consecutive stages of DSE (mean \pm SD) in patients requiring atropine administration

Dobutamine dose (μ g/kg/min)	ADRB1145A>G		p	ADRB11165C>G		p
	AA (n=17)	AG+GG (n=8)		CC (n=16)	GC+GG (n=9)	
HR 0	69.1 \pm 11.9	65.3 \pm 10.0	0.406	68.4 \pm 12.1	67.0 \pm 10.2	0.760
HR 10	71.5 \pm 12.0	72.6 \pm 12.7	0.887	74.3 \pm 12.9	67.7 \pm 9.3	0.419
HR 20	76.6 \pm 15.4	82.5 \pm 11.7	0.215	82.7 \pm 15.7	71.0 \pm 7.7	0.074
HR 30	108.6 \pm 23.4	117.3 \pm 22.4	0.406	117.1 \pm 21.5	101.1 \pm 23.1	0.108
Δ HR 0-30	39.5 \pm 23.7	52.0 \pm 23.2	0.215	48.8 \pm 23.6	34.1 \pm 22.4	0.121
SBP 0	79.1 \pm 8.1	79.6 \pm 11.5	0.977	122.4 \pm 14.0	130.4 \pm 17.3	0.276
SBP 10	79.4 \pm 8.4	76.4 \pm 12.9	0.754	123.7 \pm 16.8	135.8 \pm 11.8	0.049

SBP 20	76.9 ± 10.6	76.1 ± 13.1	0.842	131.9 ± 15.7	129.6 ± 16.3	1.000
SBP 30	80.6 ± 10.1	81.0 ± 10.2	0.842	142.0 ± 17.7	135.0 ± 15.6	0.388
ΔSBP 0-30	13.4 ± 17.4	15.9 ± 18.7	0.932	19.6 ± 16.5	4.6 ± 15.6	0.043
DBP 0	79.1 ± 8.1	79.6 ± 11.5	0.977	78.1 ± 10.1	81.2 ± 6.9	0.419
DBP 10	79.4 ± 8.4	76.4 ± 12.9	0.754	76.9 ± 10.7	81.1 ± 8.0	0.251
DBP 20	76.9 ± 10.6	76.1 ± 13.1	0.842	76.9 ± 12.0	76.1 ± 10.1	0.677
DBP 30	80.6 ± 10.1	81.0 ± 10.2	0.842	79.5 ± 11.0	82.9 ± 7.6	0.452
ΔDBP 0-30	1.5 ± 8.7	1.4 ± 15.4	0.511	1.4 ± 12.1	1.7 ± 9.0	0.846

U Mann-Whitney test

Table 7 Summary of studies of *ABCB1* polymorphism associations with hemodynamic response

<i>ADRB1</i> polymorphism	Type of subjects	Number of subjects	Type of stress	Results	Ref.
1165C>G 145A>G	patients with indications for DSE	163 (132 – Caucasians; 26 – Blacks; 7 - others)	DSE	no association between the polymorphisms and HR, SBP, DBP and magnitude of response	2
1165C>G	healthy male volunteers premedicated with atropine	30 Caucasians	DSE	association between the polymorphism and SBP	14
1165C>G 145A>G	patients with indications for exercise test	890 Caucasians	exercise test	association between <i>ADRB1</i> 1165C>G maximal SBP during exercise and SBP changes from rest to maximal	13
1165C>G 145A>G	healthy male volunteers	38 Caucasians	DSE	no association between the polymorphisms and HR, SBP	17
1165C>G 145A>G	patients with indications for DSE	144 Caucasians	DSE	no association between the polymorphisms and HR, SBP, DBP and magnitude of response	present study

DSE – dobutamine stress echocardiography, HR- heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure