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PHARMACOGENETICS

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

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Abstract
Purpose The aim of this study was to determine an association between the *ADRB1* 1165C>G and 145A>G polymorphisms and hemodynamic response [heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressure] to dobutamine during dobutamine stress echocardiography (DSE).
Methods The study involved 144 patients with clinical indications for DSE. The PCR–restriction fragment length polymorphism method was used to identify the *ADRB1* 1165C>G and 145A>G polymorphisms.
Results Heart rate during DSE increased in all analyzed study groups. Patients with the *ADRB1* 1165CC and 1165CG+GG polymorphisms demonstrated similar HR, including magnitude of response [change in heart rate (ΔHR 0–30): 42.1±17.5 vs. 46.1±15.5 bpm, respectively]. HR and ΔHR 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 in subjects with either polymorphism and did not differentiate patients with the *ADRB1* 145AA polymorphism from those with the *ADRB1* 145AG polymorphism, nor those with the *ADRB1* 1165CC polymorphism from those with the *ADRB1* 1165CG+GG polymorphism. No differences were noted in the magnitude of response, with the increase in SBP and DBP comparable in all genotypes. Similar observations were made in patients (25/144 studied) with atropine requirements during DSE.
Conclusion The *ADRB1* 1165C>G and 145A>G polymorphisms are not associated with the HR, SBP and DBP responses in Polish Caucasian patients requiring diagnostic dobutamine stress echocardiography

Keywords ADRB1 · 1165C>G and 145A>G polymorphisms · Dobutamine stress echocardiography

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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 both environmental and genetic factors. With respect to the latter, data are available that demonstrate the association of several genes, such as those encoding the beta1-adrenergic receptor [1, 2], G-protein alpha subunit [3, 4] and G-protein beta3 subunit [5], with effects on the response rate as measured by HR and BP.

The beta-adrenoreceptor system plays an important role in the regulation of the human cardiovascular system. Two common polymorphisms have been identified in the beta1-adrenergic receptor gene: *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 the differential response to β_1-agonists and antagonists in numerous studies [6–10]. However, little information has been published on the

effects of *ADRB1* polymorphisms on heart function in stress situations, and the results that have been studied are contradictory, ranging from reports of a significant association 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 the positive inotropic and chronotropic effects of dobutamine, DSE has become a popular diagnostic tool for the evaluation of coronary artery disease in patients unable to undergo standard exercise stress tests. However, based on clinical observations, there are interpersonal variations in the response to dobutamine or the exercise test in terms of HR (with some patients requiring atropine administration due to an inability to complete the test and achieve target HR) and BP response [11–13]. Polymorphisms in genes involved in regulating heart function may shed light on the observed diversity in heart response to dobutamine. One of the potential candidates is the *ADRB1* gene.

The aim of this study was to determine an association between *ADRB1* gene polymorphisms and hemodynamic response (namely, HR, SBP and the DBP) to dobutamine during DSE.

Methods

Subjects

The study cohort consisted of 144 patients of Caucasian origin (77 women, 67 men; age range 31–80 years) with a clinical indication for DSE. Of these 144 patients, 25 required atropine administration during DSE. DSE is standardly indicated for the detection of coronary artery disease in subjects who are unable to undergo standard exercise stress testing. A detailed description of the characteristics of the patients recruited for the study is presented in Table 1. The study protocol was approved by the 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 in which the administration of dobutamine is steadily increased over time (from 10, 20, 30 to 40 μg/kg/min at 3-min intervals) [15]. The HR (based on 12-lead electrocardiogram) and BP were measured at baseline (after a rest period), at the start of the dobutamine infusion period and at the end of each 3-min interval. In patients with atropine requirements, i.e. in subjects who were not able to reach target HR at a dobutamine dose of 30 μg/kg/min, the drug was administered in divided doses, beginning at 0.25 mg and increasing to 1.0 mg. Most patients evaluated reached target HR at a dobutamine level of 30 μg/kg/min, which was then taken for all subjects to be the end time-point for analysis. Each subject discontinued beta-blockers and/or calcium channel blockers at least five half-lives of the drug before study onset.

Table 1 Patient characteristics

Parameter	Patient data
Age (years)	59.3±8.8
Sex	
Female	65 (54.62)
Male	54 (45.38)
Body mass index (kg/m^2)	27.8±3.85
Smoking	19 (15.97)
Hypertension	78 (65.55)
Diabetes	15 (12.60)
Medication	
Angiotensin-converting enzyme	55 (46.22)
Acetylsalicylic acid	72 (60.50)
Beta-blockers	68 (57.14)
Ca^{2+}-blockers	23 (19.33)
Statins	68 (57.14)
Diuretics	28 (23.53)

Patient data are given as the mean ± standard deviation (SD) or as the number of patients (*n*) with the percentage of patient population given in parenthesis

Genotyping

Genomic DNA was extracted from samples of peripheral blood leukocytes according to a standard protocol. Genotyping of the *ADRB1* Arg389Gly (rs1801253, c.1165C>G in exon 1) and Ser49Gly (rs1801252, c.145A>G in exon 1) polymorphisms, using a PCR–restriction fragment length polymorphism (RFLP) method with *Bsm*FI and *Eco*0109I 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 in our analysis *ADRB1* 1165GG and 145GG homozygotes would be combined with *ADRB1* 1165GG and 145GG heterozygotes. Conformity of genotype distributions to the Hardy–Weinberg law was assessed using χ^2-test. Categorical baseline characteristics were compared between

Table 2 Resting systolic blood pressure, diastolic blood pressure and heart rate

ADRB1 polymorphism	Genotype	Mean SBP (mmHg)	p^a	Mean DBP (mmHg)	p^a	Mean HR (bpm)	p^a
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	

All values are given as the mean ± SD

SBP, Resting systolic blood pressure, DBP, resting diastolic BP; HR, heart rate

[a] Significance was determined using the Mann–Whitney U test

groups using the Fisher exact test (Statistica ver. 8.0; Statsoft Software, Warsaw, Poland). Numerical variables between groups were evaluated by the Mann–Whitney U test. A p level <0.05 was considered to be statistically significant.

Results

The patients were stratified into two groups based on the identification of the *ADRB1* 1165C>G or 145A>G polymorphism. No significant differences between the groups were found for the parameters presented in Table 1 (general patient data), namely, age, sex, body mass index (BMI), smoking habits, coexistent cardiovascular diseases and medication. Genotype and allele distributions fit the Hardy–Weinberg equilibrium in both study groups. Taking into account the observed genotype frequencies and the standard deviation (SD), for 119 patients this study has a >80% power to detect differences in SBP, DBP and HR if they exceed 9.5, 5.8 and 6.4, respectively, for the Ser49Gly polymorphism and 8.5, 5.0 and 5.5, respectively, for theArg389Gly polymorphism. For differences between starting parameters and those observed after the administration of 30 μg of dobutamine, our study has a >80% power when the difference in the mean values between genotype-stratified patients would be >11.6 (ΔSPB), 4.9 (ΔDBP) and 10.4 (ΔHR) for the Ser49Gly polymorphism and 10.0, 4.3 and 9.1, respectively, for the Arg389Gly polymorphism.

Resting hemodynamics

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

HR, SBP and DBP response during DSE

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

Table 3 Heart rate and increase in heart rate (ΔHR) at consecutive stages of DSE

Dobutamine dose (μg/kg/min)[a]	*ADRB1* 145A>G		p^b	*ADRB1* 1165C>G		p^b
	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
ΔHR 0–30	42.1±17.5	46.1±15.5	0.211	45.1±18.1	40.5±15.4	0.193

All values are given as the mean ± SD

DSE, Dobutamine stress echocardiography

[a] HR 0, 10, 20, 30, Heart rate at baseline and at 10, 20, 30 μg/kg/min dobutamine, respectively; ΔHR, Change in heart rate from baseline and the end of the experiment

[b] Significance was determined using the Mann–Whitney test U test

Table 4 Systolic blood pressureand its increase (ΔSBP) at consecutive stages of DSE

Dobutamine dose (μg/kg/min)[a]	*ADRB1* 145A>G		p^b	*ADRB1* 1165C>G		p^b
	AA (n=90)	AG (n=29)		CC (n=67)	GC+GG (n=52)	
SBP 0	133.4±15.7	133.6±16.4	0.948	132.4±15.2	134.7±16.7	0.516
SBP 10	138.5±16.0	138.2 ±16.9	0.988	137.7±16.2	139.3±16.3	0.679
SBP 20	146.7±19.4	147.6±21.7	0.861	146.2±20.0	147.8±19.9	0.796
SBP 30	150.5±20.2	150.9±27.2	0.948	149.6±22.2	151.9±21.9	0.530
ΔSBP 0-30	17.1±16.9	17.3±25.1	0.719	17.1±20.6	17.2±17.2	0.755

All values are given as the mean ± SD

[a] SBP, 10, 20, 30, Systolic blood pressure at baseline and at 10, 20 and 30 μg/kg/min dobutamine, respectively; ΔSBP 0-30, change in systolic blood pressure from baseline to end of experiment

[b] Significance was determined using the Mann–Whitney test *U* test

The SBP at all stages of DSE was similar in patients with either polymorphism and did not differentiate *ADRB1*145AA from 145AG subjects, and *ADRB1* 1165CC from 1165CG+GG cases. 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. A 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 analyzed groups of *ADRB1* polymorphisms (except for some isolated SBP measurements) (Table 6).

Discussion

The aim of this study was to define the role of the *ADRB1* 1165C>G and 145A>G polymorphisms in interindividual variability to dobutamine response during DSE (among patients with clinical indication for the test). The data currently available are not consistent regarding the associations of *ADRB1* single nucleotide polymorphisms with hemodynamic response during stress situations, including DSE. Our results did not demonstrate a significant association between the *ADRB1* 1165C>G and 145A>G polymorphisms and three parameters of hemodynamic response during DSE, i.e. HR, SBP and DBP, or with the magnitude of response of these parameters, both in patients with and without atropine requirements within the constraints of the standard DSE protocol. These observations are in keeping with the data reported by Aquilante et al. [2] who did not demonstrate any influence of the *ADRB1* 1165C>G and 145A>G polymorphisms on HR, SBP and DBP response in American Caucasians during DSE, which had been clinically indicated (with four drug half-lives of 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 the DSE protocol on HR, SBP and contractility

Table 5 Diastolic blood pressure and its increase (ΔDBP) at consecutive stages of DSE

Dobutamine dose (μg/kg/min)[a]	*ADRB1* 145A>G		p^b	*ADRB1* 1165C>G		p^b
	AA (n=90)	AG (n=29)		CC (n=67)	GC+GG (n=52)	
DBP 0	83.4±9.8	82.8±8.4	0.655	83.3±9.3	83.3±9.8	0.719
DBP 10	87.6±10.5	83.5±13.7	0.181	87.0±11.6	86.2±11.3	0.900
DBP 20	84.0±9.5	82.7±9.5	0.319	83.3±10.4	84.3±8.1	0.573
DBP 30	80.8±9.0	79.9±11.2	0.719	80.1±10.6	81.3±8.1	0.443
ΔDBP 0-30	−2.6±7.9	−2.9±8.9	0.890	−3.2±7.9	-1.9±8.4	0.664

All values are given as the mean ± SD

[a] DBP 10, 20, 30, Diastolic blood pressure at baseline and at 10, 20 and 30 μg/kg/min dobutamine, respectively; ΔDBP 0-30, change in Diastolic blood pressure from baseline to end of experiment

[b] Significance was determined using the Mann–Whitney test *U* test

Table 6 Heart rate, SBP, DBP and increase in heart rate (ΔHR), SBP (ΔSBP) and DBP (ΔDBP) at consecutive stages of DSE in patients requiring atropine administration

Dobutamine dose (μg/kg/min)	*ADRB1* 145A>G		p	*ADRB1* 1165C>G		p^a
	AA (*n*=17)	AG+GG (*n*=8)		CC (*n*=16)	GC+GG (*n*=9)	
HR 0	69.1±11.9	65.3 ±10.0	0.406	68.4±12.1	67.0±10.2	0.760
HR 10	71.5±12.0	72.6 ±12.7	0.887	74.3±12.9	67.7±9.3	0.419
HR 20	76.6±15.4	82.5 ±11.7	0.215	82.7±15.7	71.0±7.7	0.074
HR 30	108.6±23.4	117.3±22.4	0.406	117.1±21.5	101.1±23.1	0.108
ΔHR 0-30	39.5±23.7	52.0 ±23.2	0.215	48.8±23.6	34.1±22.4	0.121
SBP 0	79.1±8.1	79.6±11.5	0.977	122.4±14.0	130.4±17.3	0.276
SBP 10	79.4±8.4	76.4±12.9	0.754	123.7±16.8	135.8±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

All values are given as the mean ± SD

[a] Significance was determined using the Mann–Whitney test *U* test

parameters. These authors did not note any association between the *ADRB1* 1165C>G and 145A>G polymorphisms and HR and SBP, although 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. The findings of our study and those of Aquilante et al. [2] and Kindermann et al. [17] are in contrast to data on a German population presented by La Rosee et al. [14]. These authors evaluated the influence of the *ADRB1* 1165C>G polymorphism on hemodynamic response in healthy volunteers premedicated with atropine in order to block the parasympathetic system. They found a significant association between the *ADRB1* polymorphism and SBP, with *ADRB1* 1165CC homozygotes having a greater increase in the SBP response to dobutamine during DSE than carriers of the 1165GG polymorphism. The differences between our findings and those of Aquilante et al. [2] and La Rosee et al. [14] may possibly be attributed to

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

ADRB1 polymorphisms	Type of subjects	Number of subjects	Type of stress	Results	Reference
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 ADRB1 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

the different populations studied: those in our study and that of Aquilante et al. [2] were recruited among patients with a clinical indication for DSE, while La Rosee et al. analyzed healthy volunteers [14]. However, the negative results reported by Kindermann et al. [17] were also from a healthy population. Another factor which should be considered is the parasympathetic system blockade introduced by La Rosee et al. [14] with atropine administration; this might attenuate the genotype-related response to dobutamine in our patients and those of Aquillante et al. [2]. La Rosee et al. administered atropine to healthy volunteers prior to the study and observed effects of the *ADRB1* polymorphism under cholinergic blockade, whereas the patients from our study requiring atropine to complete the DSE were not stratified according *ADRB1* polymorphisms. HR was also not associated with the *ADRB1* 1165C>G and 145A>G polymorphisms in Finnish study conducted in patients subjected to an exercise test based on clinical indication. In this latter study, an association was noted between *ADRB1* 1165C>G maximal SBP during exercise and SBP changes from rest to maximal [13]. A summary of studies conducted on the association of hemodynamic changes during stress with the *ADRB1* polymorphisms is presented in Table 7.

The parameter which was not affected by the *ADRB1* 1165C>G polymorphism in the three studies cited above 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 the HR, SBP and DBP response in Polish Caucasian patients undergoing diagnostic dobutamine stress echocardiography.

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