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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 ( $\Delta$ HR 0-30) –  $42.1 \pm 17.5$  bpm vs.  $46.1 \pm 15.5$  bpm, respectively. Likewise, HR and  $\Delta$ 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  $\beta_1$ -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  $\beta$ -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  $\chi^2$ -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 <sup>2</sup> )      | 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 <sup>2+</sup> -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 ( $\Delta$ HR) at consecutive stages of DSE (mean±SD)

| Dobutamine dose ( $\mu$ 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 |
| $\Delta$ 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 ( $\Delta$ SBP) at consecutive stages of DSE (mean $\pm$ SD)

| Dobutamine dose ( $\mu$ 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 |
| $\Delta$ 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 ( $\Delta$ DBP) at consecutive stages of DSE (mean $\pm$ SD)

| Dobutamine dose ( $\mu$ 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 |
| $\Delta$ 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 ( $\Delta$ HR), SBP ( $\Delta$ SBP), DBP ( $\Delta$ DBP) at consecutive stages of DSE (mean $\pm$ SD) in patients requiring atropine administration

| Dobutamine dose ( $\mu$ 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        |
| $\Delta$ 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 | <b>0.049</b> |

|           |             |             |       |              |              |              |
|-----------|-------------|-------------|-------|--------------|--------------|--------------|
| 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   | <b>0.043</b> |
| 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<br>145A>G         | patients with indications for DSE                  | 163 (132 – Caucasians;<br>26 – Blacks;<br>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<br>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<br>145A>G         | healthy male volunteers                            | 38 Caucasians   | DSE            | no association between the polymorphisms and HR, SBP  | 17            |
| 1165C>G<br>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