

## Adrenoreceptor Polymorphism

# The Arg389Gly $\beta_1$ -Adrenoceptor Polymorphism and Catecholamine Effects on Plasma-Renin Activity

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<b>OBJECTIVES</b>	The purpose of this research was to find out whether, in humans, dobutamine-induced hemodynamic effects and increase in plasma-renin activity (PRA) might be $\beta_1$ -adrenoceptor ( $\beta_1$ AR) genotype-dependent.
<b>BACKGROUND</b>	In vitro Arg389Gly- $\beta_1$ AR polymorphism exhibits decreased receptor signaling.
<b>METHODS</b>	We studied 10 male homozygous Arg389- $\beta_1$ AR subjects and 8 male homozygous Gly389- $\beta_1$ AR subjects; to avoid influences of codon 49 polymorphism, all were homozygous Ser49- $\beta_1$ AR. Subjects were infused with dobutamine (1 to 6 $\mu$ g/kg/min) with or without bisoprolol (10 mg orally) pretreatment, and PRA, heart rate, contractility, and blood pressure were assessed.
<b>RESULTS</b>	With regard to PRA, dobutamine increased PRA more potently in Arg389- $\beta_1$ AR versus Gly389- $\beta_1$ AR subjects. Bisoprolol markedly suppressed the dobutamine-induced PRA increase in Arg389- but only marginally in Gly389- $\beta_1$ AR subjects. With regard to hemodynamics, dobutamine caused larger heart rate and contractility increases and diastolic blood pressure decreases in Arg389- versus Gly389- $\beta_1$ AR subjects. Bisoprolol reduced dobutamine-induced heart rate and contractility increases and diastolic blood pressure decreases more potently in Arg389- versus Gly389- $\beta_1$ AR subjects.
<b>CONCLUSIONS</b>	Codon 389 $\beta_1$ AR polymorphism is a determinant not only of hemodynamic effects but also of PRA. Thus, $\beta_1$ AR polymorphisms may be useful for predicting therapeutic responses to $\beta$ AR-blocker treatment. (J Am Coll Cardiol 2005;46:2111-5) © 2005 by the American College of Cardiology Foundation

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$\beta_1$ -adrenoceptors ( $\beta_1$ ARs) play an important role in regulation of cardiac function in man; furthermore, they are involved in lipolysis and renin secretion (1). There are two functionally important single nucleotide polymorphisms (SNPs) in the  $\beta_1$ AR gene: at position 49 serine is substituted by glycine (Ser49Gly), whereby in vitro Gly49-variant was more susceptible to agonist-mediated down-regulation than Ser49-variant. At position 389 arginine is substituted by glycine (Arg389Gly); in vitro Arg389-variant has basal and isoprenaline-activated adenylyl cyclase activity three- to four-fold higher than Gly389-variant; Gly389-variant, however, was initially considered the wild-type receptor but is the minor allele (2-5).

Controversial data exist on functional consequences of Arg389Gly- $\beta_1$ AR polymorphism in humans; in isolated human tissues, some studies found larger agonist-induced responses in Arg389- versus Gly389- $\beta_1$ AR, whereas others failed to find genotype-dependent differences (5,6). Similarly, in vivo several groups failed to find, in homozygous Arg389- or Gly389- $\beta_1$ AR subjects, differences in exercise-induced heart rate (HR) increases mediated by cardiac  $\beta_1$ AR (6,7). La Rosee et al. (8), however, using a modified

dobutamine stress echocardiography protocol, demonstrated recently that homozygous Arg389- $\beta_1$ AR subjects exhibited larger inotropic and blood pressure (BP) responses than subjects carrying one or two Gly389 alleles. In contrast to all exercise studies published so far, however, La Rosee et al. (8) administered dobutamine to subjects pretreated with atropine to exclude possible counter-regulatory parasympathetic effects.

In contrast to cardiac effects, little is known about the possible impact of  $\beta_1$ AR polymorphisms on extracardiac effects such as renin secretion, that, in humans, is mediated by renal  $\beta_1$ AR (1). We could not find genotype-dependent differences in exercise-induced increase in plasma-renin activity (PRA) in Arg389- versus Gly389- $\beta_1$ AR subjects (9). The renin-angiotensin-aldosterone system (RAAS) plays an important role in BP regulation and is certainly one target, out of several, for BP-lowering effects of  $\beta$ AR-blockers (10). Thus, it could well be that antihypertensive effects of  $\beta$ AR-blockers are modulated by  $\beta_1$ AR polymorphisms (11).

In this study we determined, in male homozygous Arg389- or Gly389- $\beta_1$ AR subjects, the effects of dobutamine on PRA and its attenuation by the  $\beta_1$ AR selective blocker bisoprolol to find out whether there are genotype-dependent differences. Studies were performed in the absence of atropine to find out whether atropine is necessary for demonstration of  $\beta_1$ AR genotype-dependence of dobutamine-

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**Abbreviations and Acronyms**

$\beta_1$ AR = beta<sub>1</sub>-adrenoceptor  
 BP = blood pressure  
 DBP = diastolic blood pressure  
 HR = heart rate  
 PRA = plasma-renin activity  
 QS<sub>2c</sub> = heart rate-corrected duration of the electromechanical systole  
 RAAS = renin-angiotensin-aldosterone system  
 SBP = systolic blood pressure  
 SNP = single nucleotide polymorphism

evoked effects (8). Codon 49 SNP can modulate functional responsiveness of codon 389 SNP (12); therefore, all subjects participating in this study were homozygous Ser49- $\beta_1$ AR.

**METHODS**

**Genotyping.** To obtain human genomic deoxyribonucleic acid (DNA), 10 ml of blood was withdrawn in ethylenediaminetetraacetic acid (EDTA) tubes, and DNA was extracted with the GenomicPrep Blood DNA Isolation Kit (Amersham Biosciences, Buckinghamshire, United Kingdom);  $\beta_1$ AR genotypes at codon 49 and 389 were determined by polymerase chain reaction and subsequent restriction length polymorphism (restriction enzymes *Sau96I* and *BstNI*, respectively) with modified protocols from previously described methods (3,4).

**Experimental protocol.** We genotyped 201 subjects for  $\beta_1$ AR codon 49 and 389 SNPs (Ser49Gly and Arg389Gly); 18 male subjects participated in the study (Table 1). Ten were homozygous Arg389 (mean age 25 ± 3 years), eight were homozygous Gly389 (mean age 25 ± 3 years), and all were homozygous Ser49.

All study participants gave written informed consent. The ethical committee of the University of Essen Medical School approved the study protocol. Subjects were in normal health, based on cardiovascular and other medical history, physical examination, and biochemical, hematologic, and electrocardiographic screening. No subjects took any medication, and all were nonsmokers. Subjects and investigators were

blinded for  $\beta_1$ AR haplotype. All subjects were studied in the morning in supine position after an overnight fast. Subjects were advised to avoid caffeine, alcohol, and physical exercise before each study. Room temperature was kept stable between 24°C to 26°C.

Subjects were studied on two separate days with at least a one-week interval; after arrival at the clinical laboratory at 7:30 AM and after affixment of instruments, indwelling polythene catheters were positioned in right and left antecubital veins. Blood samples were drawn from the right arm; drugs were separately administered in the left arm.

After 1 h of rest in the supine position, subjects were intravenously infused with dobutamine (DobutaminSolvay/Solvay Arzneimittel, Hannover, Germany) in doses of 1, 2, 4, and 6  $\mu$ g/kg/min for 15 min each (13). For bisoprolol (Concor, Merck, Darmstadt, Germany) experiments, subjects received a 10-mg tablet orally 150 min before the infusion started.

We assessed PRA and cardiovascular effects of dobutamine immediately before bisoprolol intake, immediately before start of infusion, and during the last 5 min of each dobutamine dose. Cardiovascular effects were assessed by determining systolic (SBP) and diastolic BP (DBP), HR, and systolic time intervals exactly as described elsewhere (9). From systolic time intervals, only data for HR-corrected duration of electromechanical systole (QS<sub>2c</sub>) are shown, which is the most sensitive parameter for contractility changes (14).

For PRA and plasma bisoprolol determination, 10-ml ice-cold EDTA blood was withdrawn at the given time points; PRA was assessed by radioimmunoassay (DiaSorin, Saluggia, Italy), and bisoprolol plasma levels were assessed by the high-pressure liquid chromatography method.

**Statistics.** Data given in text and figures are mean values ± SEM of the number of experiments. Differences between baseline values of HR, QS<sub>2c</sub>, SBP, DBP, and PRA were assessed by the unpaired two-tailed Student *t* test.

Dose-response curves of dobutamine-induced changes in HR, contractility, BP, and PRA were analyzed by factorial analysis of variance (ANOVA) (factors: dobutamine dose and bisoprolol pretreatment or haplotype) with Bonferroni's post-test for multiple comparisons.

**Table 1.** Baseline Parameters in Subjects Homozygous for Arg389- or Gly389- $\beta_1$ AR Before and After Oral Pretreatment With 10 mg Bisoprolol

	Arg389 $\beta_1$ AR (n = 10)		Gly389 $\beta_1$ AR (n = 8)	
	Before	After Bisoprolol	Before	After Bisoprolol
PRA (ng/ml/h)	1.5 ± 0.2	0.8 ± 0.2*	1.5 ± 0.2	0.8 ± 0.1*
HR (beats/min)	53 ± 2	45 ± 2*	51 ± 3	45 ± 2*
BP <sub>syst</sub> (mm Hg)	119 ± 3	111 ± 4*	121 ± 3	114 ± 4*
BP <sub>diast</sub> (mm Hg)	75 ± 4	73 ± 4	77 ± 1	75 ± 2
QS <sub>2c</sub> (ms)	511 ± 6	515 ± 6	513 ± 4	515 ± 2

Baseline parameters were assessed after 1 h of rest in supine position or 150 min after oral application of 10 mg bisoprolol (see Methods section). Mean ± SEM of 10 (Arg389) and 8 (Gly389) experiments. \*p < 0.05 vs. corresponding values before bisoprolol.

AR = adrenoceptor;  $\beta_1$ AR = beta<sub>1</sub>-adrenoceptor; BP<sub>diast</sub> = diastolic blood pressure; BP<sub>syst</sub> = systolic blood pressure; HR = heart rate; ng/ml/h = ng angiotensin I formed/ml/h; PRA = plasma-renin activity; QS<sub>2c</sub> = heart rate-corrected duration of electromechanical systole.

Effects of maximum dobutamine dose or bisoprolol on resting parameters were analyzed by a paired two-tailed Student *t* test.

To assess bisoprolol effects on dobutamine-induced changes in HR, contractility, BP, and PRA for each dobutamine dose, individual differences in hemodynamic or PRA changes measured in the presence and absence of bisoprolol were calculated and analyzed by factorial analysis of variance (factors: dobutamine dose and haplotype) with Bonferroni's post-test for multiple comparisons.

Power calculations for the primary end point, a delta maximal PRA increase of 1.0 ng angiotensin I formed/ml/h, revealed with the given number of 10 Arg389- $\beta_1$ AR and 8 Gly389- $\beta_1$ AR subjects a power of 75%. Statistical calculations were performed with GraphPad Prism 4.0 and GraphPad StatMate 2.0 programs (GraphPad Software, San Diego, California). A *p* value <0.05 was considered statistically significant.

## RESULTS

From 201 subjects genotyped, 53% were homozygous Arg389, 10% homozygous Gly389, and 37% heterozygous Arg389Gly; thus, allele frequencies with Gly as a minor allele (*f*(-) = 0.28) were in agreement with previous reports and in Hardy-Weinberg equilibrium (5,6,8,9).

Basal hemodynamic parameters and PRA were not significantly different between Ser49Arg389- $\beta_1$ AR and Ser49Gly389- $\beta_1$ AR subjects (Table 1).

**Effects of dobutamine. PRA.** Dobutamine infusion caused dose-dependent PRA increases that were significantly larger in Arg389- versus Gly389- $\beta_1$ AR subjects (Fig. 1). Maximal PRA increase was  $1.56 \pm 0.32$  ng angiotensin I formed/ml/h in Arg389- and  $0.60 \pm 0.20$  ng/ml/h in Gly389- $\beta_1$ AR subjects (*p* < 0.05, Bonferroni adjustment with four comparisons) (Fig. 1).

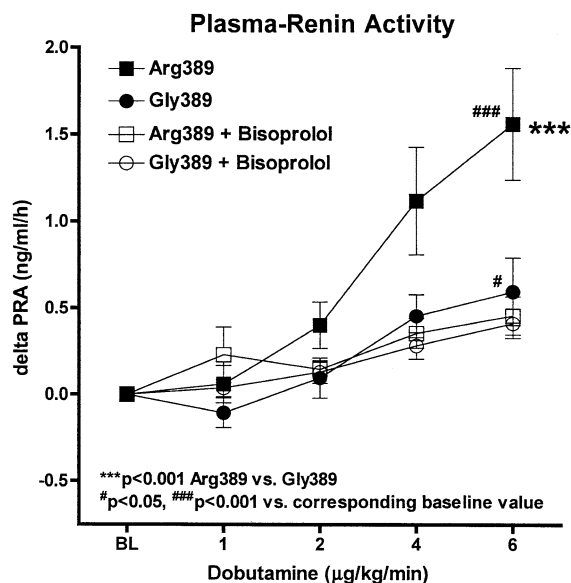
**HR, CONTRACTILITY, AND BP.** Dobutamine infusion dose-dependently increased HR (Fig. 2), contractility ( $QS_2c$ ) (Fig. 2), and SBP (Fig. 3), and decreased DBP (Fig. 3).

Maximal increases in HR ( $12.9 \pm 2.0$  beats/min vs.  $5.2 \pm 1.5$  beats/min) and contractility ( $-97.0 \pm 4.6$  ms vs.  $-79.1 \pm 6.1$  ms) were significantly larger in Arg389- versus Gly389- $\beta_1$ AR subjects. A similar tendency of larger effects in Arg389- versus Gly389- $\beta_1$ AR subjects was also found for dobutamine-induced maximal DBP decreases, but this did not reach statistical significance. Maximal SBP increases, however, showed no genotype-dependent difference (Fig. 3).

**Effects of bisoprolol on dobutamine effects.** A total of 150 min after 10 mg bisoprolol orally, plasma bisoprolol levels were  $48.5 \pm 5.3$  ng/ml in Arg389- and  $49.7 \pm 1.9$  ng/ml in Gly389- $\beta_1$ AR subjects.

Bisoprolol significantly decreased basal PRA, HR, and SBP, slightly prolonged  $QS_2c$ , but only marginally affected DBP (Table 1).

Bisoprolol markedly suppressed the dobutamine infusion-induced PRA increase in Arg389- $\beta_1$ AR subjects



**Figure 1.** Dobutamine infusion-induced plasma-renin activity (PRA) increase in 10 healthy homozygous Arg389- $\beta_1$ AR subjects (squares) and 8 homozygous Gly389- $\beta_1$ AR subjects (circles) before (closed symbols) and after (open symbols) treatment with bisoprolol ( $1 \times 10$  mg orally 150 min before infusion). Ordinate: PRA increase in  $\Delta$  ng angiotensin I formed/ml/h. Abscissa: dobutamine dose in  $\mu$ g/kg/min for 15 min each. BL = baseline.

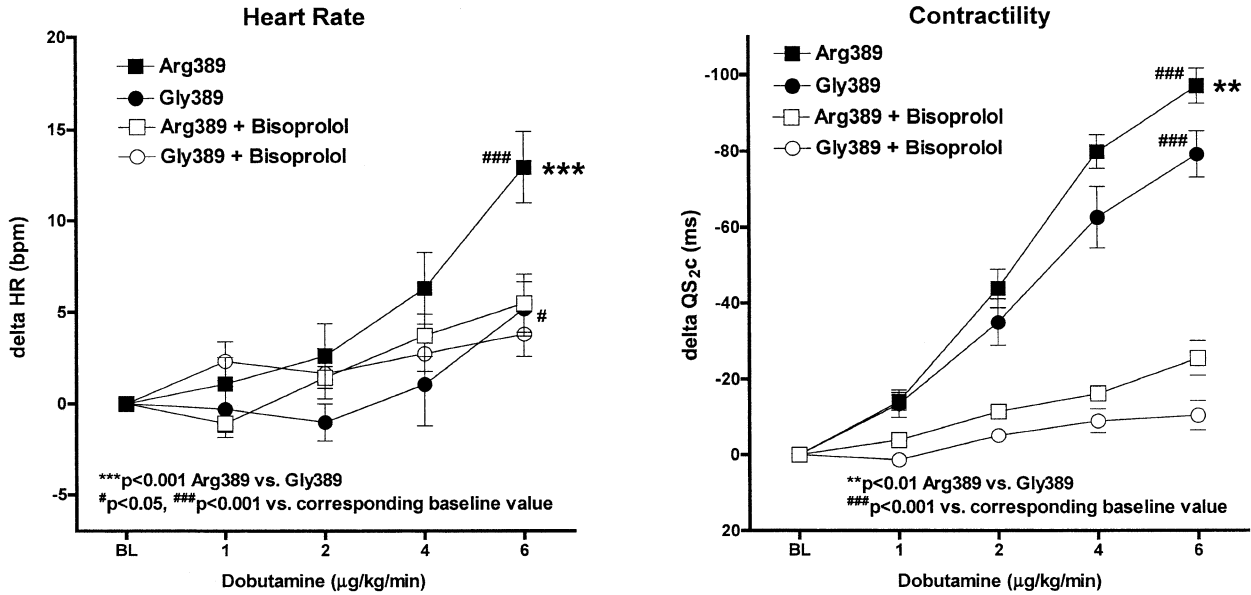
but did not significantly affect the dobutamine-induced (weak) PRA increase in Gly389- $\beta_1$ AR subjects (Fig. 1).

Moreover, bisoprolol markedly suppressed the dobutamine infusion-induced HR increase in Arg389- $\beta_1$ AR subjects, but did not significantly affect the (weak) dobutamine-induced HR increase in Gly389- $\beta_1$ AR subjects (Fig. 2).

Similarly, bisoprolol reduced the dobutamine-induced contractility increase and DBP decrease at most dobutamine doses more pronounced in Arg389- versus Gly389- $\beta_1$ AR subjects, although this was not statistically significant at all dobutamine doses (Figs. 2 and 3). Attenuation of the dobutamine-induced SBP increase by bisoprolol, however, was not genotype-dependent (Fig. 3).

## DISCUSSION

The new finding of this study is that the  $\beta_1$ AR agonist dobutamine evoked, via renal  $\beta_1$ AR stimulation (1), significantly larger PRA increases in homozygous Arg389- $\beta_1$ AR subjects than in homozygous Gly389- $\beta_1$ AR subjects. Moreover, the  $\beta_1$ AR-blocker bisoprolol inhibited dobutamine-evoked PRA increases significantly more potently in Arg389- versus Gly389- $\beta_1$ AR subjects. This might have important clinical implications:  $\beta$ AR-blockers are first-line drugs for treatment of hypertension. Although the experience of antihypertensive treatment with  $\beta$ AR-blockers has existed for nearly 40 years, the mechanism of their BP-lowering effects is still not completely understood (10). Among various hypotheses, RAAS inhibition might play an important role. Thus, various authors showed that BP-lowering effects of  $\beta$ AR-blockers were better the higher PRA was (10). From the present results it can be predicted



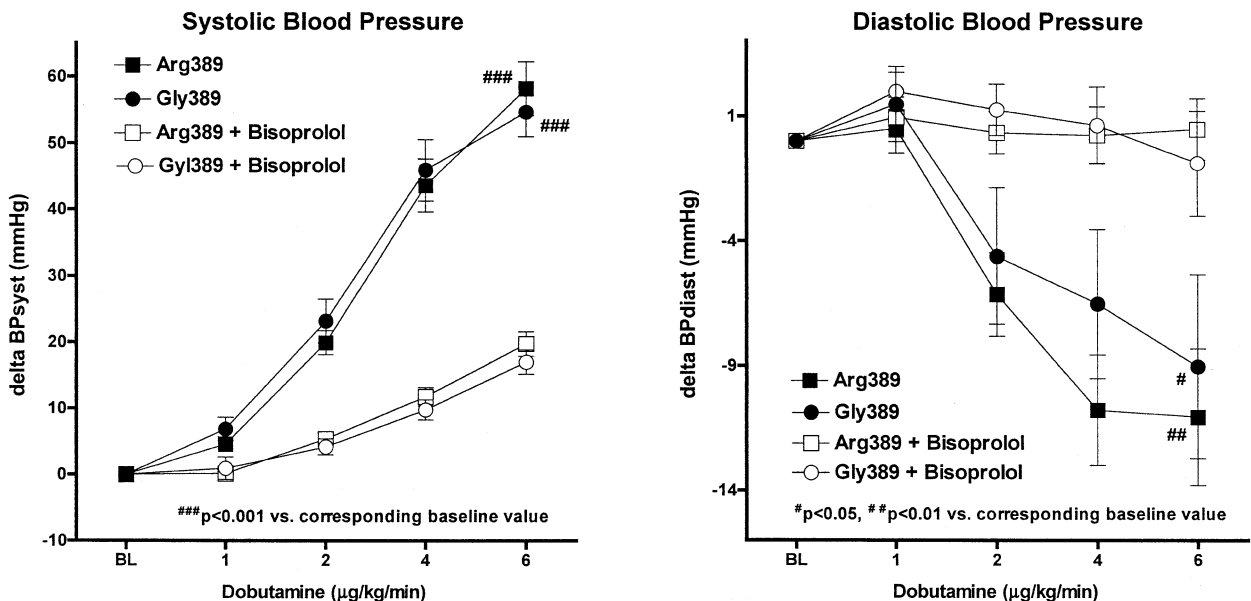
**Figure 2.** Dobutamine infusion-induced heart rate (HR) (left) and contractility increases (right) in 10 healthy homozygous Arg389- $\beta_1$ -adrenoceptor (AR) subjects (squares) and 8 homozygous Gly389- $\beta_1$ AR subjects (circles) before (closed symbols) and after (open symbols) treatment with bisoprolol ( $1 \times 10$  mg orally 150 min before infusion). Ordinates, left: heart rate (HR) increase in  $\Delta$  beats/min (bpm), right: contractility increase (HR-corrected duration of electromechanical systole [ $QS_2c$ ] shortening) in  $\Delta$  ms. Abscissa: dobutamine dose in  $\mu\text{g}/\text{kg}/\text{min}$  for 15 min each. BL = baseline.

that Arg389- $\beta_1$ AR patients should have a good response to  $\beta$ AR-blocker treatment, whereas Gly389- $\beta_1$ AR patients should be poor or non-responders.

In our study dobutamine evoked larger HR and contractility increases in Arg389- than in Gly389- $\beta_1$ AR subjects, in accordance with recent findings in chronic heart failure that exercise capacity was significantly better in Arg389- than in Gly389- $\beta_1$ AR patients (15). Similarly, La Rosee et al. (8) found, in subjects pretreated with atropine, that those

homozygous Arg389- $\beta_1$ AR exhibited larger SBP and contractility responses to dobutamine than those carrying one or two Gly389 alleles. Our data now clearly show that atropine pretreatment is not necessary because also *in the absence of atropine* dobutamine caused significantly larger cardiac effects in Arg389- versus Gly389- $\beta_1$ AR subjects.

In contrast to  $\beta_1$ AR genotype-dependent dobutamine effects ([8], present data), in several studies exercise-induced HR and contractility increases were not different between



**Figure 3.** Dobutamine infusion-induced systolic blood pressure (BP<sub>syst</sub>) (left) and diastolic blood pressure (BP<sub>diast</sub>) changes (right) in 10 healthy homozygous Arg389- $\beta_1$ -adrenoceptor (AR) subjects (squares) and 8 homozygous Gly389- $\beta_1$ AR subjects (circles) before (closed symbols) and after (open symbols) treatment with bisoprolol ( $1 \times 10$  mg orally 150 min before infusion). Ordinates, left: BP<sub>syst</sub> changes in  $\Delta$  mm Hg, right: BP<sub>diast</sub> changes in  $\Delta$  mm Hg. Abscissa: dobutamine dose in  $\mu\text{g}/\text{kg}/\text{min}$  for 15 min each. BL = baseline.

Arg389- and Gly389- $\beta_1$ AR subjects (6). Preliminary data from our group indicate that this also holds true for subjects treated with atropine.

The reason for this discrepancy in cardiac responses to exercise versus dobutamine is not completely understood. However, it should be considered that: 1) responses to exercise are strongly dependent on the physical fitness of test subjects, and it is extremely difficult to precisely control for that. Hence, subjects participating in exercise studies may be of different physical fitness, and that would evoke unpredictable results. 2) Exercise may induce more physiologic responses, whereas dobutamine infusion may induce more pharmacologic responses. 3) In all exercise studies published so far, subjects were not controlled for codon 49 SNP. Codon 49 SNP, however, can modulate functional responsiveness of codon 389 SNP; accordingly,  $\beta_1$ AR haplotype analysis could be more important than single SNP analysis (12,16). Thus, differences obtained in exercise versus dobutamine studies could also be due to  $\beta_1$ AR haplotype inhomogeneity of study groups. In our study, however, all subjects were homozygous Ser49- $\beta_1$ AR.

Recent evidence suggested that subjects exhibited larger BP and HR responses to  $\beta_1$ AR-blockers if they carried Arg389- $\beta_1$ AR, and this could be modulated by codon 49 SNP (11,16). Similarly, in chronic heart failure, long-term  $\beta$ AR-blocker treatment improved left ventricular ejection fraction significantly better in Arg389- than in Gly389- $\beta_1$ AR patients (17,18). However, no genotype-dependent differences during  $\beta$ AR-blocker treatment were also published (19,20). In our study bisoprolol inhibited all dobutamine-induced hemodynamic changes, with the exception of SBP changes, in Arg389- $\beta_1$ AR subjects more potently than in Gly389- $\beta_1$ AR subjects. Thus, our data might be taken as a further indication that  $\beta_1$ AR polymorphisms might predict hemodynamic responses to  $\beta$ AR-blocker treatment (11).

**Conclusions.** Dobutamine infusion causes larger PRA, HR, and contractility increases in Arg389- than in Gly389- $\beta_1$ AR subjects. In addition, the  $\beta_1$ AR-blocker bisoprolol inhibited PRA and cardiac responses to dobutamine more potently in Arg389- versus Gly389- $\beta_1$ AR subjects. Thus,  $\beta_1$ AR polymorphisms may be useful to predict therapeutic responses to  $\beta$ AR-blocker treatment.

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