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Association of β_1 and β_2-adrenoceptor polymorphisms with the demand for inotropic catecholamine support following CABG surgery

Abstract

Hemodynamic instability is a common complication in the first hours following cardiac surgery and inotropic catecholamine support is an acceptable treatment strategy for its management. β_1 and β_2-adrenoceptors (β_1 and β_2 AR) are mediated the positive inotropic and chronotropic responses of the heart to catecholamines. Previous evidence has suggested an association between β_1 and β_2AR polymorphisms and cardiac response and change in receptor signaling. This study aimed to evaluate the relationship between β_1 and β_2AR polymorphisms with the demand for catecholamine inotropic support among coronary artery bypass grafting (CABG) patients. One hundred ninety-eight consecutive patients who underwent CABG with cardiopulmonary bypass were included in this study. We assessed hemodynamic parameters, dose, and duration of inotropic support according to β_1 and β_2AR genotypes in the post-operative period. DNA genotyping was assessed through polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and PCR genotyping results were confirmed by direct DNA sequencing. Our results indicated that patients carrying one or two alleles of the Arg389-β_1AR variant required significantly shorter inotropic support time compared with patients homozygous for the Gly389-β_1AR ($p=0.003$). Finally, neither β_1AR polymorphisms nor Arg16Gly-β_2AR polymorphisms are associated with catecholamine-induced hemodynamic effects. These findings suggest that genetic variability in the β_1 and β_2AR polymorphisms may not be a major determinant of cardiac responses to catecholamine treatment in the Iranian population. However, larger-scale studies with different ethnicities are needed for confirmation.

Keywords: *β-adrenoceptors, Coronary artery bypass grafting, Hemodynamic response, Inotropic support, Polymorphism*

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Introduction

Background

Hemodynamic disturbances and impaired cardiac functions are major problems and causes of death following coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (CPB) that is secondary to myocardial hypoxia or ischemia [1]. The condition is manifested by cardinal signs such as hypotension, peripheral vasoconstriction, and oliguria. The mechanism of post-operative hypotension is incompletely understood. It is believed that systemic inflammation and vasoplegia that occur in patients following major cardiac surgery manifest as systemic arterial vasodilation and profound hypotension with a high cardiac index and a low systemic vascular resistance [2]. Inotropic support by catecholamines is the cornerstone treatment of hypotensive post-CABG states to improve blood pressure and organ perfusion via increasing cardiac output with an effect on beta and alfa adrenergic receptors. However, in many patients who experience post-CABG depressed myocardial function, inadequate and weak response to catecholamines is observed and identification of patients who will adequately respond to inotrope therapy remains a challenge [3].

β_1-adrenergic pathway through positive inotropic and chronotropic effects plays a key role in the regulation of heart rate and contractility and is responsive to the effects of circulating catecholamines [4]. In addition, β_2-adrenoceptors (β_2ARs) are also expressed in the myocardium, atria of the heart, and vascular smooth muscle beds. β_2ARs are allowed for calcium influx in response to cardiac sympathetic nerve activity, leading to positive inotropic and chronotropic effects [5]. Recent in vivo and in vitro studies have shown multiple genetic variants in β_1 and β_2ARs [6]. This implies that variations in the β_1 and β_2AR genes might explain some variability observed in the response of the patient's CABG surgery to inotropic support therapy.

Enhanced left ventricular ejection fraction and also greater stroke volume, cardiac output, and mean arterial pressure has been observed in healthy subjects homozygous for the Gly16-β_2AR allele [7]. Additionally, previous studies (Bruck et al., 2005, La Rosée et al., 2004) have demonstrated a higher heart rate and/or contractility among individuals homozygous for the Arg389-β_1AR variant compared with other codons 389 genotype carriers [8, 9]. A study done by Leineweber et al., 2007, in a sample of the German population showed that less post-surgical inotropic support is required in patients undergoing CABG who were preoperatively chronically treated with metoprolol and homozygous for the Arg389-β_1AR, than those with one or two Gly389-β_1AR alleles [10]. Over-responsiveness to propranolol has been reported in the Iranian population that may be associated with polymorphism of β-adrenoceptors [11]. Furthermore, it was observed that the Arg16Gly-β_2AR genotype may have a protective effect on hypertension in comparison with the Arg16Arg-β_2AR variant in the Iranian population [12].

Therefore, the present study was designed to investigate whether the hemodynamic responses to inotropic support by epinephrine in Iranian patients with hemodynamic instability following CABG surgery with CPB are influenced by β_1 and β_2AR polymorphic variations.

Methods

Study population

This prospective study included 198 patients attending Mazandaran Heart Center, Sari, Iran between April and September 2018. The patients aged 18 years or older and indicated for elective CABG surgery with CPB that received inotropic support only by epinephrine after weaning from CPB or in the first 12 hours after postoperative ICU admission were included in this study. The patients who needed a pacemaker, intra-aortic balloon pump after weaning from CPB, those who also had post-operative major bleeding (> 200 ml/h first 6 h after surgery), septic shock, and preoperative end-stage renal disease or post-operative severe renal failure (creatinine clearance < 30 ml/min/1.73 m^2) requiring temporary hemodialysis were also excluded from the study. The study protocol was approved by the ethics committee of Mazandaran University of Medical Sciences.

Data collection and clinical assessment

Pre and post-operative demographics, medical history, and operative details were extracted from the patient's medical records. Preoperatively, the usual doses of cardiac medications were prescribed for all participants and none received inotropic support.

A systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure (MAP) < 65 mmHg was considered as the post-operative hypotension that required inotropic support. Inotropic support by epinephrine was started at the rate of 10 ng/kg/min and titrated against blood pressure to achieve the hemodynamic target of mean arterial pressure between 70 and 90 mmHg.

At the time when the inotrope infusion was initiated, systolic and diastolic blood pressure (DBP), mean arterial pressure, heart rate (HR), central venous pressure (CVP), and urine output were recorded. During the inotrope infusion, these parameters were frequently monitored. In addition, the required dose and total duration of epinephrine infusion were recorded. To maintain adequate circulating volume and electrolyte balance during inotrope administration, all patients received intravenous isotonic fluids.

DNA extraction

Five milliliters of peripheral venous blood samples were taken in tubes containing ethylene diamine tetraacetic acid (EDTA) and preserved at -80 °C for isolation of DNA. Genomic DNA was extracted using a column-based DNA isolation kit (Denazist Asia Co., Mashhad, Iran) according to the manufacturer's instructions. The concentration and purity of the extracted DNA were measured using a Nanodrop spectrophotometer (Biochrom WPA Biowave II^+ UV/visible spectrophotometer, Cambridge, UK).

Genotyping using PCR-RFLP method

A polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis was performed to determine the β_1AR gene polymorphisms (codon 389, nucleotide 1165, and codon 49, nucleotide 145) and β_2AR gene polymorphism (codon 16, nucleotide 46). PCR was performed using 200 ng of template DNA, 10 µl Taq DNA polymerase 2x master mix RED (Amplicon A/S, Odense, Denmark) containing 150 mM Tris-HCl pH 8.5, 40 mM $(NH_4)_2SO_4$, 3 mM $MgCl_2$, 0.2% Tween 20, 0.4 mM of each dNTP and 0.2 U/µl Ampliqon Taq DNA polymerase, along with 10 pmol of specific primers, and 7 µl nuclease-free water. The PCR condition, sequence of primers, and expected product lengths are listed in Table 1. The PCR products were restriction-digested with 10 U/µl of *Bcg*I (β_1AR codon 389), *EcoO109*I (β_1AR codon 49) (Fermentas; Thermo Fisher Scientific, Inc., Waltham, MA, USA) at 37˚C for 3 hours and *BsrD*I (β_2AR codon 16) (Bio Lab; New England) at 55˚C for 3 hours. Digested fragments were analyzed by electrophoretic separation on 2% agarose gel containing DNA green fluorescent dye (DenaZist, Mashhad, Iran) (Fig. 1). The staff of the ICU and the investigators were blinded to the genotypes of the patients.

PCR products sequencing

The genotypes determined by PCR-RFLP were further confirmed by direct sequencing (Fig. 1). Genotyping was performed without knowing the population study status. Ten percent of random samples were tested by Sanger sequencing with forward and reverse primers by ABI 3130XL.

Statistical analysis

The data were analyzed by SPSS Statistics software, version 22 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were quoted as mean ± standard deviation (SD) and the results of the categorical measurements were expressed as numbers and percentages. The Chi-square test and Fisher's exact test were used for categorical variables. Differences between means were compared using the one-way analysis of variance (ANOVA). Post-hoc analysis was performed when ANOVA indicated significance. $P<0.05$ was considered a statistical difference in each test.

Results

The mean age of patients was 62.1 ± 10.1 years (65.7% male). One hundred ninety-eight patient samples were genotyped for Arg389Gly-β_1AR (rs1801253) and Ser49Gly-β_1AR (rs1801252) polymorphisms and 162 patient samples for Arg16Gly-β_2AR (rs1042713) polymorphism.

Among all participants, the allele frequency for the Gly389-β_1AR and Ser49-β_1AR alleles were 53% and 90%, respectively, and also for Arg389-β_1AR and Gly49-β_1AR alleles were 47% and 10%, respectively. Furthermore, the frequency of Arg16-β_2AR and Gly16-β_2AR alleles were 15.7% and 84.3%, respectively. Regarding the genotypes found in our population, 52 patients (26.3%) undergoing CABG surgery with CPB were homozygous for Gly at position 389 (Gly389Gly), 105 patients (53%) heterozygous for Arg389Gly, and 41 (20.7%) homozygous for Arg at position 389 (Arg389Arg). The genotype frequencies of Ser49Gly-β_1AR polymorphism were Ser49Ser (80.3%), Ser49Gly (19.2%), and Gly49Gly (0.5%). Moreover, genotyping revealed a prevalence of homozygous patients for Arg16Arg of 6.8%, heterozygous for Arg389Gly of 17.9%, and homozygous for Gly389Gly of 75.3%.

Baseline demographics, operative details, and post-operative clinical information of patients according to β_1 and β_2AR genotypes are listed in Tables 2 and 3, respectively. Baseline characteristics were similar in all variants (Table 2). As illustrated in Table 3, operative details and postoperative data were similar between the study population with different polymorphisms. However, regarding the Arg16Gly-β2AR polymorphism, post-operative left ventricular ejection fraction (LVEF) was significantly higher in patients with the Arg16Arg genotype with 55 ± 5.5% versus 48.5 ± 9.2% in patients with Arg16Gly and 51.1 ± 7% in Gly16Gly carriers ($p=0.028$). There was no statistically significant difference in postoperative LVEF between the two β_1AR polymorphisms.

Hemodynamic variables and changes in hemodynamic parameters as compared to baseline after the initiation of epinephrine infusion are presented in Table 4 and Fig. 2. The results showed that increases in SBP, DBP, MAP, and HR were similar after inotropic support by epinephrine and there were no significant differences between the three polymorphisms studied. Similar results were also obtained for a decrease in CVP according to β_1 and β_2AR genotypes. Although Gly389Gly-β_1AR and Gly16Gly-β_2AR homozygous and Ser49Gly-β_1AR heterozygous patients had a higher change in HR compared to other variants, no significant differences were found between the three βAR polymorphisms. Furthermore, the increase in SBP and MAP and decrease in CVP were, in patients heterozygous for the Ser49Gly-β_1AR variant, higher than in patients with other variants. However, these changes were small and not statistically significant (Table 4, Fig. 2). As can be seen from Fig. 2, in patients carrying one or two Arg alleles at codon 389, the duration of inotropic support after CABG surgery with CPB was significantly shorter ($P< 0.05$) than in patients homozygous for the Gly389-β_1AR. There was a trend towards a lower dose of epinephrine required to achieve the hemodynamic goal in patients homozygous for the Arg389-β_1AR, Ser49-β_1AR, and Gly16-β_2AR variants compared to other genotypes, although this difference just failed to reach statistical significance.

Discussion

Poor cardiac function and post-operative hypotension during the early hours after CABG surgery with CBP are associated with several serious complications including vasospasm, generalized inflammatory response, organ dysfunction, and an increased risk of death [13]. Epinephrine is an effective initial inotropic agent that is widely used in patients with hypotension following cardiac surgery and improves cardiac output and myocardial performance [14]. However, among post-cardiac surgery patients, different responses to inotropic agents were observed. Beta-adrenoceptors mediate the physiological effects of catecholamines and also these receptors are polymorphic. Hence, inter-individual differences in genetic composition could lead to various drug responses and it could give rise to innovative effective treatment approaches. Although previous studies (Leineweber et al., 2007, Dhein et al., 2017) have proven the significant association between the β_1AR gene and its polymorphisms in cardiovascular diseases and their impact on responses to βAR agonist treatment, still its role as a therapeutic determinant remains unclear [10, 15]. According to our knowledge, there have been neither previous investigations of the genetic basis of hemodynamic effects of positive inotropic agents in patients undergoing CABG surgery with CPB in the Iranian population. Results of our study suggest a lack of any association between the three polymorphisms studied and the patient's hemodynamic response to inotropic support after CABG surgery with CPB. In addition, patients carrying one or two Arg389-β_1AR alleles needed significantly less inotropic support time compared to Gly389-β_1AR homozygotes.

Evidence suggests that mutant Arg389Arg-β_1AR is a known genetic risk factor for cardiovascular diseases [16]. In the present study, we found that 41 (20.7%) patients were carrying mutant Arg389Arg-β_1AR genotype, which is lower than the reported frequency in other white populations [15, 17]. Regarding the genotypes found in our population, the homozygous Gly49Gly-β_1AR variant was observed only in one patient. The Gly49Gly variant is extremely rare and its lower frequency was also reported in previous studies within various ethnic populations [18-20]. Furthermore, in good accordance with our data, Gly16-β_2AR and Gly16Gly-β_2AR were reported as the most prominent alleles and genotypes among different ethnic populations (White and Black Americans, Chinese and Egyptian populations) [21, 22].

The Gly389-β_1AR has a 3-4-fold fewer isoprenaline stimulation of the adenylyl cyclase than the Arg389-β_1AR variant [8]. Accordingly, patients carrying the Arg389-β_1AR allele would be expected more responsive to inotropic therapy and also need lower doses of catecholamine than others. This is following the findings of a study by Dhein et al., 2017, that also reported more norepinephrine requirements in patients with the Gly389 variant of the β_1AR compared to those carrying one or two Arg389-β_1AR alleles [15]. In addition, Leineweber et al., 2007, also found that the Gly389Gly-β_1AR variant was significantly associated with a higher required dose of epinephrine to reach a stable and comparable hemodynamic response [10]. However, the results of our study were in disagreement with data obtained from the above-mentioned studies. The present data showed that the dose of epinephrine needed for improvement of cardiac function in patients homozygous for Arg389-β_1AR was two times higher than for subjects homozygous for Gly389-β_1AR. On the other hand, patients who carried Gly389Gly-β_1AR genotype responded two times more to inotropic support therapy in comparison with patients homozygous for Arg at codon 389, although this just failed to reach statistical significance (p=0.703). According to our findings, it may be postulated that there is an Arg389Gly-β_1AR gene-dose effect.

It was reported that the time of inotropic support was the shortest in patients homozygous for the Arg allele at codon 389, compared to patients homozygous for the Gly389-β_1AR variant [10]. This is in good accordance with to present data. Our results demonstrated that the time of inotropic support to achieve a positive inotropic response was significantly shortest in Arg389Gly-β_1AR heterozygous and Arg389Arg-β_1AR homozygous patients (p=0.003). Furthermore, compared with the reported inotrope infusion time in Leineweber et al., 2007 study, the mean inotropic support time was relatively shorter in the current study (2.71 vs 20.5 hours in Arg389Arg-β_1AR and 6 vs 10.5 hours in Gly389Gly-β_1AR) [10].

Present findings did not show any statistically significant association between hemodynamic measurements (SBP, MAP, CVP, HR) and β_1AR variants at codon 389 in patients receiving inotropic support (p=0.0.922, p=0.807, p=0.974, and p=0.274, respectively). Similarly, the influence of the Arg389Gly-β_1AR polymorphism on modified hemodynamic responses to epinephrine and norepinephrine in young healthy adults was not observed [23, 24]. It is worth noting that several studies on the importance of genetic variations of β_1AR on hemodynamic responses yielded conflicting results. In this context, in a study (Bruck et al., 2005) comparing cardiac responses to β_1AR stimulation by rather β_1AR selective agonist dobutamine in healthy subjects, improvement of cardiac function was superior in the cardiac contractility and blood pressure in individuals carrying the Arg389Arg-β_1AR homozygous than the subjects carrying the Gly389Gly-β_1AR variant [8]. Moreover, administration of dobutamine in subjects homozygous for the Arg389-β_1AR caused significantly larger increases in heart rate compared to carriers of one or two alleles of the Gly389-β_1AR [6, 9]. These differences may be postulated that inter-individual variations in the required time to improve cardiac function and hemodynamic response to inotropic support after cardiac surgery might be associated with other different genetic mutations and variations of the adrenergic system.

According to the results of our study, the Ser49Gly-β_1AR polymorphism has no significant influence on SBP, MAP, CVP, and HR (p=0.505, p=0.309, p=0.859, and p=0.179, respectively). This is consistent with the findings of Kumar et al., 2008, who found that Ser49Gly-β_1AR polymorphism did not alter the cardiac response and also systolic and diastolic blood pressures among South Indians [25]. Ser49Ser-β_1AR was found to be associated with a higher mean HR under resting conditions, which might result in a higher heart rate as we observed for Ser49Ser-β_1AR genotype carriers, although this just failed to reach statistical significance (p=0.179) (Fig. 2) [26]. In our inotropic support patients with the Ser49Ser-β_1AR variant, a lower dose of epinephrine was required to achieve a positive inotropic response than the Ser49Gly-β_1AR genotype. Meanwhile, the Gly49 variant of the β_1-adrenoceptor gene was shown to be associated with much higher desensitization and faster down-regulation of the β_1-adrenoceptors [27]. On the other hand, in the current study, patients with the Ser49Ser-β_1AR variant responded better to the inotropic support than those carrying the Gly49-β_1AR allele; however, there was no significant difference between the two variant carriers (p=0.831).

In vitro studies exhibited that the Gly16-β_2AR allele enhanced βAR down-regulation [28]. Following this theory, this down-regulation would be expected to decrease heart rate and also attenuate the effects of inotropic and chronotropic

catecholamines. This might result in a higher required dose of epinephrine in patients carrying one or two Gly16-β_2AR alleles as observed in our study. By contrast, present findings demonstrated that an increase in heart rate in response to βAR stimulation by epinephrine in Arg16Arg-β_2AR patients was less than in other β_2AR variants. However, we did not find any association between the Arg16Gly-β_2AR polymorphism and increases in heart rate (p=0.314). This was in line with previous studies performed in young healthy subjects that failed to find any significant genotype-dependent differences between homozygous for the Arg16 or Gly16-β_2AR in male volunteers with increases in heart rate and contractility induced by terbutaline infusion [29, 30]. Down-regulation of β_2AR genotype may occur genotype independently at a similar level among all patients; this would explain a similar response to inotropic support observed in the current study.

A previous study (Snapir et al., 2003) has shown that systemic infusions of βAR agonist (epinephrine) are associated with larger vasodilation in subjects homozygous for the Arg16-β_2AR compared to those carrying one or two Gly16 alleles [31]. Theoretically, this larger vasodilation could be related to lower MAP or SBP in Arg16Arg-β_2AR homozygotes but our study failed to find any influence of the Arg16Gly-β_2AR polymorphism on hemodynamic parameters (SBP, p=0.839 and MAP, p=0.0.669). It might be due to other compensatory cardiovascular reflexes which may have overshadowed the agonist activity of catecholamines.

Taken together, chronotropic and inotropic effects of epinephrine were similar across all the different genotypes studied. Findings of the current research and several previous studies have demonstrated variable results [10, 15]. The reasons for these differences are not clearly defined, but may be related to differences in genetic properties of various races.

Limitations

The sample size of this study was relatively limited. It must be recognized that the lack of impact of these polymorphisms on the hemodynamic response of post-CABG surgery patients observed in the present study is only hypothesis-generating and further research with a bigger sample size and different ethnic backgrounds is certainly needed to give more reliable data for the general population of Iranian patients. Our study demonstrated that the number of study male participants was almost double the number of female patients which indicates that these results may be generalizable and applicable to male patients. As of now, several functionally important SNPs in the human β_1 and β_2AR coding region have been described. Hence, evaluation of the other SNPs, particularly in the β_2AR coding region such as Gln27Glu and Thr164Ile polymorphisms would have provided additional important information.

Conclusion

To conclude, our results demonstrated that in patients undergoing CABG surgery with CPB who carried one or two alleles of the Arg389-β_1AR, the time of inotrope support to achieve positive inotropic response was significantly shortest than in Gly389-β_1AR homozygotes. Furthermore, data from this study revealed that no significant association between patients' hemodynamic response to inotropic support after CABG surgery and the three polymorphisms studied has been observed in the Iranian population. However, to provide stronger evidence further genetic analysis with different and larger populations is required.

Abbreviations

AR: Adrenoceptor; CABG: Coronary artery bypass grafting; CPB: Cardiopulmonary bypass; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MAP: Mean arterial pressure; CVP: Central venous pressure; HR: Heart rate; ICU: Intensive care unit; EDTA: Ethylene diamine tetraacetic acid; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism, BMI: Body mass index, LVEF: Left ventricular ejection fraction; Clcr: Creatinine clearance; MI: Myocardial infarction; COPD: Chronic obstructive pulmonary disease; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; LMCA: Left main coronary artery; CCT: Cross-clamp time; CPBT: Cardiopulmonary bypass time; MV: Mechanical ventilation

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Authors' contributions

GE designed the study and edited the manuscript. RG and VH aided in the recruitment of the patients. AHO, OA, and RA performed the genotyping and RFLP-PCR experiments. MM analyzed the data. SE was involved in collecting clinical data and manuscript writing. All authors read and approved the contents of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the author for correspondence upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Mazandaran University of Medical Sciences (approval code:

IR.MAZUMS.REC.1397.1810). All participants provided written voluntary informed consent before the study.

Consent for publication

Not Applicable.

Competing interests

The authors declare that they have no competing interests.

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β1-and β2-adrenoreceptors on hemodynamic responses to adrenaline. Clin Sci. 2003;104:509-20.

Table 1 PCR[a] condition and characteristics of polymorphisms, primers used, and length of digested products

SNP[b]/ rs name	Primers sequence (5′→ 3′)	PCR product size	PCR conditions	Length of digested products
Arg389Gly	F[c]: CATCATGGGCGTCTTCACGC	547 bp	98 °C: 3min, followed by 35 cycles at	GG: 547
rs1801253	R[d]: TGGGCTTCGAGTTCACCTGC		98 °C: 30s, 60 °C:1min, 72 °C:30s	GC: 547,342,171,34
				CC: 342,171,34
Ser49Gly	F: CCGGGCTTCTGGGGTGTTCC	562 bp	98 °C: 3min, followed by 35	AA: 562
rs1801252	R: GGCGAGGTGATGGCGAGGTAGC		cycles at 98 °C: 45s, 60 °C:1min, 72	AG: 562,343,219
			°C:30s	GG: 343,219
Arg16Gly	F: CTTCTTGCTGGCACGCAAT	200 bp	94 °C: 3min, followed by 35	GG: 108,56,23,14
rs1042713	R: CCAGTGAAGTGATGAAGTAGTTGG		cycles at 94 °C: 1min, 54 °C:1min,	GA: 131,108,56,23,14
			72 °C:1min, 72 °C: 5min	AA: 131,56,14

a *Polymerase chain reaction*, b *Single nucleotide polymorphism*, c *Forward primer*, d *Reverse primer*

Table 2 Baseline characteristics of patients according to Arg389Gly-β_1AR, Ser49Gly-β_1AR, and Arg16Gly-β_2AR polymorphisms

Characteristics	Gly389Gly (n = 52)	Arg389Gly (n = 105)	Arg389Arg (n = 41)	Ser49Ser (n = 159)	Ser49Gly (n = 38)	Gly49Gly (n = 1)	Arg16Arg (n = 11)	Arg16Gly (n = 29)	Gly16Gly (n = 122)
Sex (male/female), n	34/18	70/35	26/15	105/54	24/14	1/0	8/3	14/15	85/37
Age (year)	62.1 ± 10.4	62.8 ± 9.9	60.4 ± 10.2	62.3 ± 10.1	62.1 ± 9.4	47	62.4 ± 9.3	60.3 ± 11.1	62.3 ± 9.7
BMI[a] (kg/m^2)	26.9 ± 4.3	26.8 ± 4.3	27.7 ± 3.6	27 ± 4.3	26.9 ± 3.5	28	26.6 ± 4.2	26.5 ± 4.6	26.9 ± 4
EuroScore II	2.1 ± 1.5	2 ± 1.7	1.6 ± 1.1	2 ± 1.7	1.7 ± 0.9	1.6	1.5 ± 0.9	2.4 ± 1.9	1.9 ± 1.4
Smoking, n	14 (26.9%)	30 (28.6%)	12 (29.3%)	45 (28.3%)	10 (26.3%)	1 (100%)	2 (18.2%)	11 (37.9%)	35 (28.7%)
Preoperative LVEF[b] (%)	51.3 ± 6.6	52.2 ± 6.7	53.9 ± 5.6	52.5 ± 6.5	51.5 ± 6.7	50	53.6 ± 6.7	50.3 ± 6.7	52.5 ± 6.4
Clcr[c] (ml/min/1.73 m^2)	71.9 ± 22.5	71.2 ± 20.2	78.9 ± 20.1	72.4 ± 20.8	74.4 ± 20.5	117	73.4 ± 21.1	70.9 ± 21.5	72.7 ± 21
Comorbid features, n									
Previous MI[d]	9 (17.3%)	15 (14.3%)	6 (14.6%)	25 (15.7%)	5 (13.2%)	0	2 (18.2%)	5 (17.2%)	18 (14.8%)
Hypertension	35 (67.3%)	66 (62.9%)	29 (70.7%)	106 (66.7%)	24 (63.2%)	0	5 (45.5%)	22 (75.9%)	81 (66.4%)
Diabetes mellitus	26 (50%)	39 (37.1%)	14 (34.1%)	67 (42.1%)	12 (31.6%)	0	6 (54.5%)	11 (37.9%)	50 (41%)
Dyslipidemia	22 (42.3%)	53 (50.5%)	16 (39%)	76 (47.8%)	15 (39.5%)	0	4 (36.4%)	11 (37.9%)	59 (48.4%)
COPD[e]	1 (1.9%)	4 (3.8%)	2 (4.9%)	5 (3.1%)	2 (5.3%)	0	0	1 (3.4%)	6 (4.9 %)
Medication status, n									
β-blocker	43 (82.7%)	95 (90.5%)	34 (82.9%)	140 (88.1%)	31 (81.6%)	1 (100%)	9 (81.8%)	26 (89.7%)	104 (85.2%)
ACE[f] inhibitor	21 (40.4%)	55 (52.4%)	19 (46.3%)	83 (52.2%)	16 (42.1%)	0	2 (18.2%)	13 (44.8%)	62 (50.8%)
ARB[g]	17 (32.7%)	30 (28.6%)	12 (29.3%)	45 (28.3%)	13 (34.2%)	0	3 (27.3%)	9 (31%)	35 (28.7%)
Diuretic	18 (34.6%)	32 (30.5%)	12 (29.3%)	50 (31.4%)	12 (31.6%)	0	4 (36.4%)	9 (31%)	37 (30.3%)
Digoxin	1 (1.9%)	1 (1%)	3 (7.3%)	3 (1.9%)	1 (2.6%)	0	0	1 (3.4%)	3 (2.5%)
Hemodynamic status (before surgery)									
HR[h] (beats/min)	70.9 ± 9.7	70.3 ± 8.5	68.7 ± 10.4	70.3 ± 9.4	69.1 ± 8.3	78	70 ± 11.2	70 ± 7.5	70.5 ± 9.3
SBP[i] (mmHg)	129.5 ± 9.4	129.8 ± 8	132.6 ± 7.3	129.8 ± 7.7	132.5 ± 10.4	132	126.5 ± 5.9	129.6 ± 9.2	129.8 ± 8.4
DBP[j] (mmHg)	81 ± 4.4	81.4 ± 4.4	82.4 ± 4.8	81.4 ± 4.5	81.8 ± 4.3	83	78.5 ± 3.5	80.7 ± 3.7	81.5 ± 4.7
MAP[k] (mmHg)	97.2 ± 5.3	97.5 ± 5.2	99.1 ± 4.3	97.5 ± 5	98.7 ± 5.6	99.3	94.5 ± 4.1	97 ± 5	97.6 ± 5.1

a *Body mass index*, b *Left ventricular ejection fraction*, c *Creatinine* clearance, d *Myocardial infarction*, e *Chronic obstructive pulmonary disease*, f *Angiotensin-converting enzyme*, g *Angiotensin receptor blocker*, h *Heart rate*, i *Systolic blood pressure*, j *Diastolic blood pressure*, k *Mean arterial pressure*

Values are presented as mean ± SD where appropriate

Not significant for all variables

Table 3 Operative details and postoperative data of patients according to Arg389Gly-β_1AR, Ser49Gly-β_1AR, and Arg16Gly-β_2AR polymorphisms

Characteristics	Gly389Gly (n = 52)	Arg389Gly (n = 105)	Arg389Arg (n = 41)	Ser49Ser (n = 159)	Ser49Gly (n = 38)	Gly49Gly (n = 1)	Arg16Arg (n = 11)	Arg16Gly (n = 29)	Gly16Gly (n = 122)
LMCA[a] disease, n	7 (13.5%)	15 (14.3%)	4 (9.8%)	22 (13.8%)	3 (7.9%)	1 (100%)	0	3 (10.3%)	17 (13.9%)
Grafts per patient, n	3.5 ± 0.9	3.4 ± 0.8	3.3 ± 0.6	3.4 ± 0.8	3.5 ± 0.6	3	3.3 ± 0.6	3.2 ± 0.7	3.4 ± 0.8
Operation time (h)	4.1 ± 0.9	4 ± 1	4 ± 0.8	4.1 ± 0.9	3.8 ± 0.8	4	4.6 ± 1	4.2 ± 1.3	4 ± 0.8
CCT[b] (min)	62.5 ± 32.7	57.4 ± 28.2	54.2 ± 21.9	59.6 ± 29.8	52.6 ± 20.4	31	73.4 ± 46.3	66.6 ± 28.2	56.2 ± 27.9
CPBT[c] (min)	97 ± 43.4	89 ± 42	89.3 ± 39.6	93.1 ± 44.6	83.5 ± 27	75	113.9 ± 63.5	108.1 ± 57.8	88.3 ± 37.4
Post-operative LVEF[d] (%)	51.6 ± 6.8	50.8 ± 8	51.2 ± 7.8	50.9 ± 7.9	52.2 ± 6.5	50	55 ± 5.5*	48.5 ± 9.2	51.1 ± 7
Time on MV[e] (h)	15.3 ± 8.2	15.1 ± 8.3	12.4 ± 6.9	14.5 ± 8	14 ± 6.7	16	16.2 ± 8.6	16.5 ± 8.1	14.5 ± 8.6

a *Left main coronary artery*, b *Cross-clamp time*, c *Cardiopulmonary bypass time*, d *Left ventricular ejection fraction*, e *Mechanical ventilation*

Values are presented as mean ± SD where appropriate

*$p < 0.05$ vs. other variants ($p=0.028$)

Table 4 Hemodynamic status of patients before initiation of inotropic support and changes induced by inotropic support according to Arg389Gly-β_1AR, Ser49Gly-β_1AR, and Arg16Gly-β_2AR polymorphisms

	Gly389Gly (n = 52)	Arg389Gly (n = 105)	Arg389Arg (n = 41)	Ser49Ser (n = 159)	Ser49Gly (n = 38)	Gly49Gly (n = 1)	Arg16Arg (n = 11)	Arg16Gly (n = 29)	Gly16Gly (n = 122)
HR[a] (beats/min)									
Baseline	87.6 ± 13.6	86.4 ± 10.8	88.1 ± 12.8	86.6 ± 11.7	87.9 ± 11.8	88	83.3 ± 12.1	85.7 ± 11.9	87.9 ± 11.8
Response	98.9 ± 12.1	95.2 ± 11.9	96.2 ± 12.2	96.7 ± 12.2	94.2 ± 11.7	98	89.4 ± 12.1	95.3 ± 13.9	97.8 ± 11.1
SBP[b] (mmHg)									
Baseline	80.5 ± 7.7	80.6 ± 6.2	81.5 ± 4.7	81.1 ± 6.5	78.1 ± 5.9	84	82.8 ± 5.9	80.8 ± 4.8	80.4 ± 6.9
Response	105.5 ± 7.9	106.7 ± 8.2	107.1 ± 10.1	106.3 ± 7.9	107.1 ± 10.9	108	107 ± 9.6	105.9 ± 9.7	106.5 ± 7.9
DBP[c] (mmHg)									
Baseline	48.7 ± 4.2	48.2 ± 5.1	48.5 ± 3.9	48.5 ± 4.9	47.3 ± 3.4	48	50.1 ± 2.3	47 ± 4.8	48.5 ± 4.8
Response	57.9 ± 3.2	58.8 ± 5.6	59.4 ± 5.2	58.4 ± 4.6	60.3 ± 6.4	51	57.3 ± 3.7	57.2 ± 4.3	59.3 ± 5.2
MAP[d] (mmHg)									
Baseline	70.1 ± 6.3	69.9 ± 5.1	70.5 ± 3.2	70.4 ± 5.3	67.9 ± 4.4	72	71.9 ± 4.1	69.9 ± 4.4	69.8 ± 5.6
Response	89.6 ± 5.5	90.7 ± 6.6	91.2 ± 8.2	90.3 ± 6.2	91.5 ± 8.6	89	90.4 ± 6.8	89.6 ± 7.4	90.8 ± 6.3
CVP[e] (cm H_2o)									
Baseline	14.8 ± 3.6	15.6 ± 3.2	14.6 ± 3.9	15.1 ± 3.3	16.4 ± 4.1	16	13.7 ± 4.1	14.7 ± 3.1	15.6 ± 3.4
Response	10.6 ± 4.7	12.1 ± 4.5	10.5 ± 5.1	11.3 ± 4.5	12.1 ± 5.6	12	9.9 ± 5.2	11.1 ± 4.8	11.7 ± 4.5

a *Heart rate*, b *Systolic blood pressure*, c *Diastolic blood pressure*, d *Mean arterial pressure*, e *Central venous pressure*

Values are presented as mean ± SD

Not significant for all variables

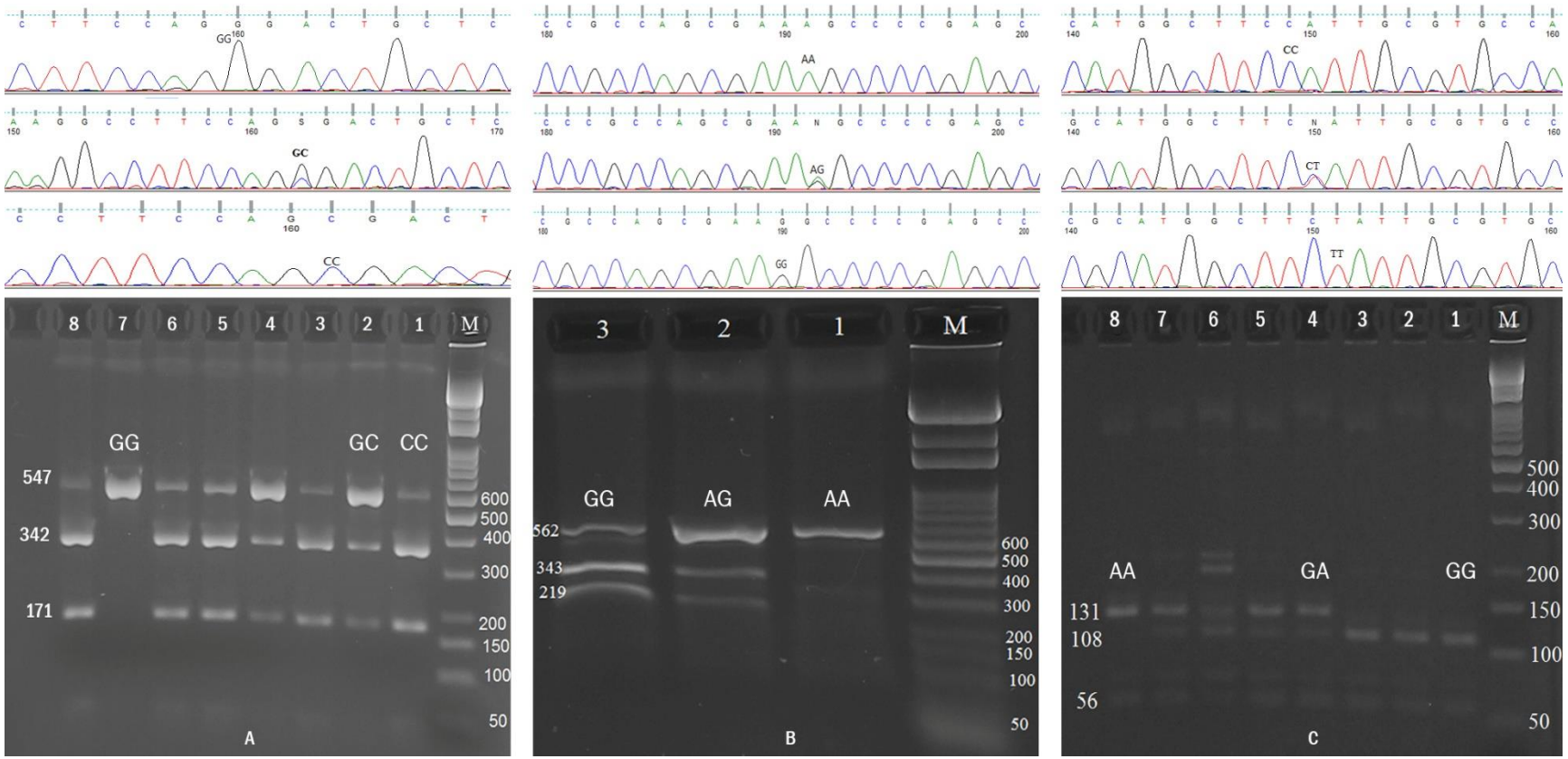
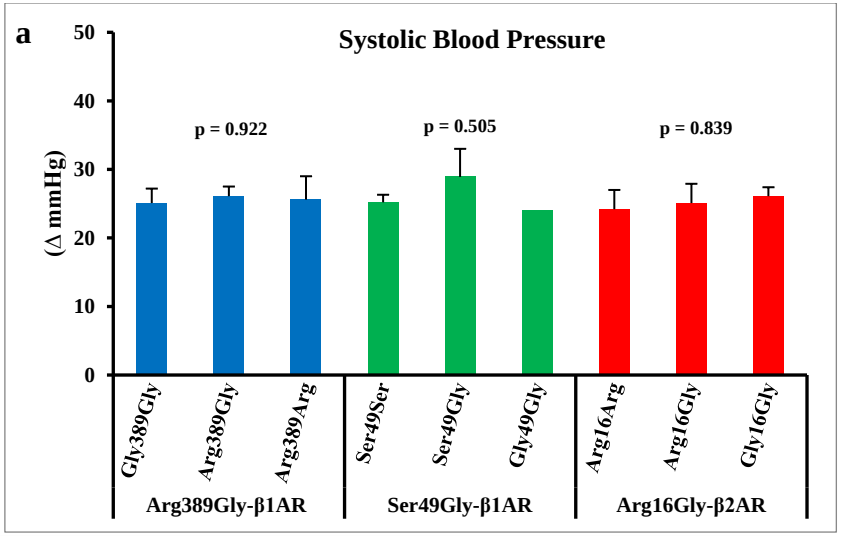
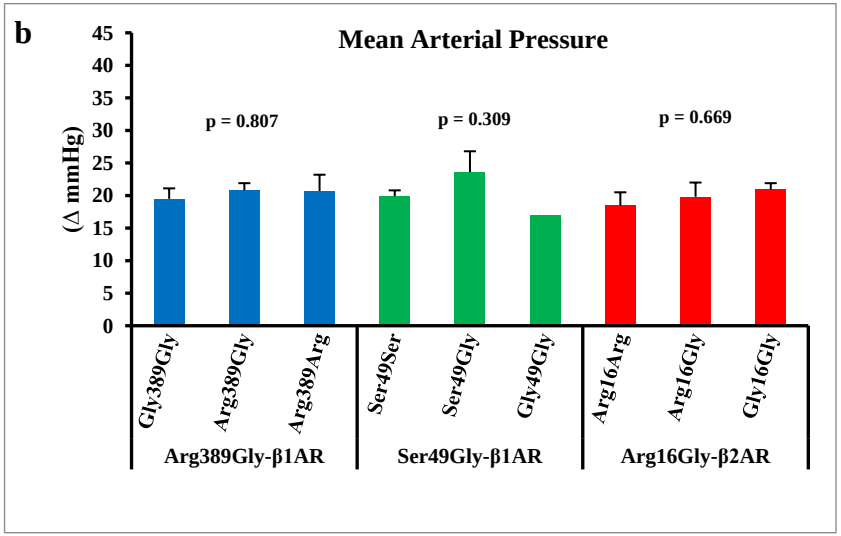
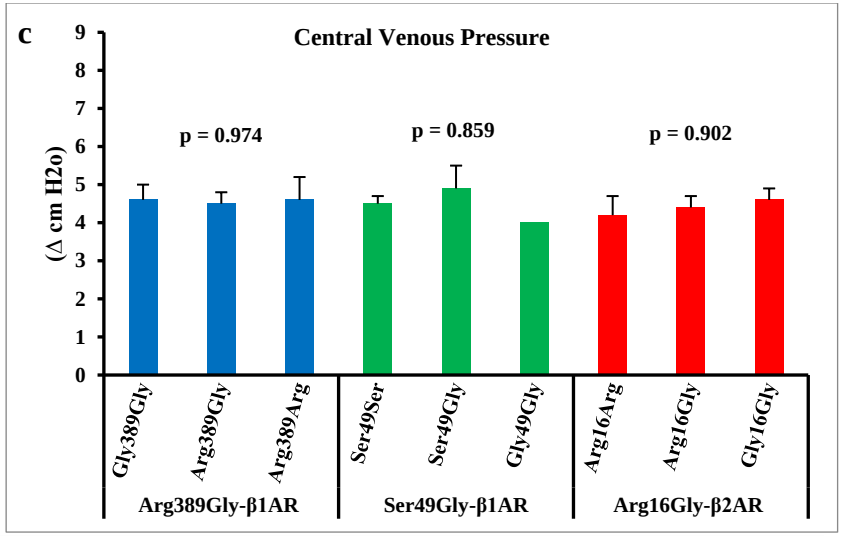
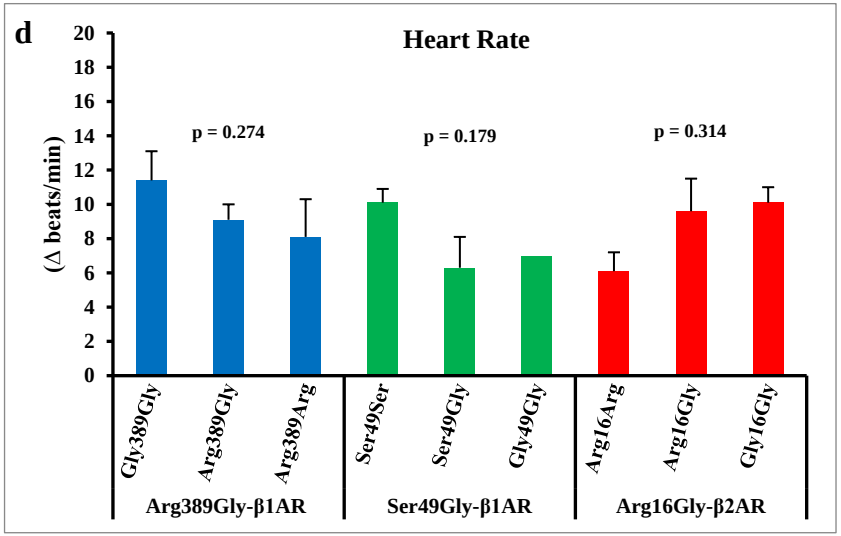


Fig. 1 Sequence analysis and pattern of 2% agarose gel electrophoresis of DNA samples for Arg389Gly-β_1AR (A), Ser49Gly-β_1AR (B), and Arg16Gly-β_2AR (C) polymorphisms detected by PCR-RFLP; Lane M shows 50bp DNA ladder; (A) the Arg389Gly GG genotype was evident as a single 547 bp fragment, GC genotype as 547,342, 171 and 34 bp fragments and CC genotype as 342, 171 and 34 bp fragments; (B) the Ser49Gly AA genotype was evident as a single 562 bp fragment, AG genotype as 562, 343 and 219 bp fragments and GG genotype as 343 and 219 bp fragments; (C) the Arg16Gly GG genotype was evident as 108, 56, 23 and 14 bp fragments, GA genotype as 131, 108, 56, 23 and 14 bp fragments and AA genotype as 131, 56 and 14 bp fragments (the reverse direction); Electrofluorogram representing all heterozygous and homozygous condition of the β_1 and β_2-adrenoceptor alleles (Top).


a
Systolic Blood Pressure
(Δ mmHg)
50
40
30
20
10
0
p = 0.922
p = 0.505
p = 0.839
Gly389Gly
Arg389Gly
Arg389Arg
Ser49Ser
Ser49Gly
Gly49Gly
Arg16Arg
Arg16Gly
Gly16Gly
Arg389Gly-β1AR
Ser49Gly-β1AR
Arg16Gly-β2AR


b
Mean Arterial Pressure
(Δ mmHg)
45
40
35
30
25
20
15
10
5
0
p = 0.807
p = 0.309
p = 0.669
Gly389Gly
Arg389Gly
Arg389Arg
Ser49Ser
Ser49Gly
Gly49Gly
Arg16Arg
Arg16Gly
Gly16Gly
Arg389Gly-β1AR
Ser49Gly-β1AR
Arg16Gly-β2AR


c
Central Venous Pressure
(Δ cm H2o)
p = 0.974
p = 0.859
p = 0.902
Gly389Gly
Arg389Gly
Arg389Arg
Ser49Ser
Ser49Gly
Gly49Gly
Arg16Arg
Arg16Gly
Gly16Gly
Arg389Gly-β1AR
Ser49Gly-β1AR
Arg16Gly-β2AR


d
Heart Rate
(Δ beats/min)
p = 0.274
p = 0.179
p = 0.314
Gly389Gly
Arg389Gly
Arg389Arg
Ser49Ser
Ser49Gly
Gly49Gly
Arg16Arg
Arg16Gly
Gly16Gly
Arg389Gly-β1AR
Ser49Gly-β1AR
Arg16Gly-β2AR

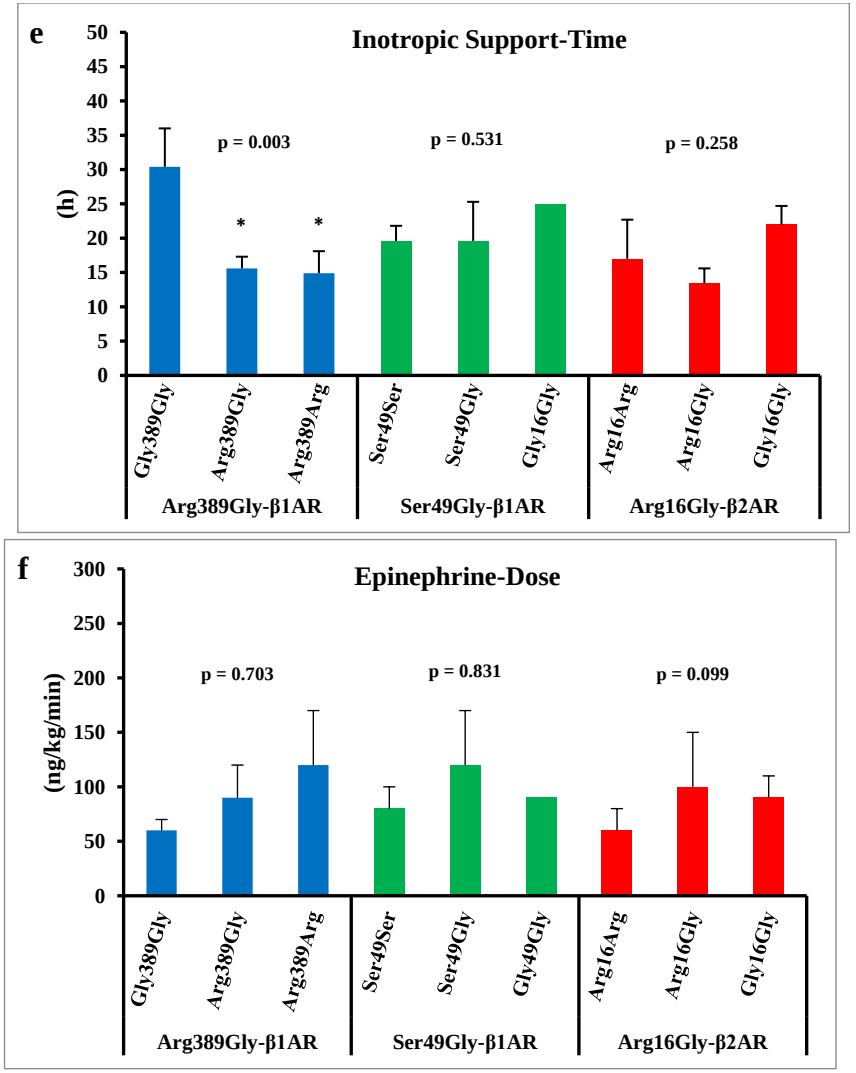


Fig. 2 Effects of the Arg389Gly-β_1AR, Ser49Gly-β_1AR, and Arg16Gly-β_2AR polymorphisms on the changes in hemodynamic parameters, dose, and duration of inotropic support in post-CABG patients. [a. increase in systolic blood pressure (Δ mmHg), b. increase in mean arterial pressure (Δ mmHg), c. decrease in central venous pressure (Δ cm H_2o), d. increase in heart rate (Δ beats/min), e. inotropic support-time (h), and f. epinephrine-dose (ng/kg/min)]. Columns are mean and the vertical bars show the SEM. Significance is indicated by an asterisk (*p< 0.05 vs Gly389Gly).