Orthostatic Blood Pressure Dysregulation and Polymorphisms of β-Adrenergic Receptor Genes in Hypertensive Patients

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The genetic susceptibility to orthostatic blood pressure dysregulation remains poorly understood. The association between polymorphisms of beta-adrenergic receptor (*β-AR*) genes and orthostatic blood pressure dysregulation in hypertensive patients was investigated. Two polymorphisms of β_1*-AR* (Arg389/Gly) and β_2*-AR* (Arg16/Gly) were genotyped in untreated hypertensive patients and normotensive patients. In patients with untreated hypertension, the frequency of β_1*-AR* Gly389 homozygote was significantly higher in patients with orthostatic hypotension (OH) ($P<.0001$) and lower in patients with orthostatic hypertension (OHT) ($P=.002$) as compared with patients with orthostatic normotension (ONT) even after Bonferroni correction. After analysis by sex and adjustment for conventional risk factors, the β_1*-AR* Gly389 homozygote conferred about a 3-fold risk of OH and independently predicted a 6.5 mm Hg greater orthostatic SBP decrease (GG -8.9 ± 13 mm Hg vs CC+CG -2.4 ± 12 mm Hg, $P<.001$) only in female hypertensive patients. The association of β_2*-AR* Arg16/Gly with OH was not significant after adjustment for conventional risk factors. In normotensive patients, no association was identified between these two polymorphisms and OHT or OH. These results indicated that the β_1*-AR* Arg389/Gly polymorphism may be associated with increased risk of OH in female hypertensive patients. *J Clin Hypertens (Greenwich).* 2014;16:207–213. ©2014 Wiley Periodicals, Inc.

Orthostatic blood pressure (BP) change is a common clinical problem in the real world of clinical practice. According to the updated consensus statement by the European Federation of Neurological Societies, orthostatic hypotension (OH) is defined as a sustained reduction in systolic BP (SBP) of at least 20 mm Hg or diastolic BP (DBP) of 10 mm Hg from the supine position to standing.[1] The most commonly used criterion for a diagnosis of orthostatic hypertension (OHT) appears to be an increase of SBP of 20 mm Hg with orthostatic change.[2] OH has been identified as an independent risk factor for cardiovascular disease,[3] arterial stiffness,[4] and ischemic stroke[5] as a potential indicator underlying autonomic dysfunction.[6] OHT is associated with cardiovascular disease,[7] sustained hypertension,[8] diabetes mellitus,[9] and target organ damage.[10] Hypertension, with estimates of heritability ranging from 31% to 68%,[11] has been associated with the increased risk of OH and OHT in many epidemiological studies.[12,13] Therefore, better understanding of the underlying pathophysiology and genetic background may predict cardiovascular events and mortality independently of traditional risk factors and might have major clinical significance in hypertensive and normotensive patients.

Many genetic variants have been suggested that partly contribute to the variation of BP response to postural change. Past studies indicate that genes on chromosome 13q and 18q are possibly associated with SBP response to postural change.[14,15] Some mitochondrial DNA mutations are also associated with idiopathic OH.[16] The sympathetic nervous system (SNS) and the renin angiotensin system (RAS) may be involved in the pathogenesis of orthostatic dysregulation of BP.[1] Although the genetic variants in genes encoding components of the RAS have been associated with hypertension and BP variations, our previous study did not find any evidence for the role of angiotensin-converting enzyme (ACE) and ACE2 in the genetic predisposition to OH or OHT in hypertensive and normotensive patients.[17] β-Adrenergic receptor (AR) is the important component of the SNS and it plays a crucial role in BP regulation.[18] There are β_1-, β_2-, and β_3*-ARs*. β_1- and β_2*-AR* are the predominate receptors in the human heart.[19] Some genetic variants in the β_1- and β_2*-AR* genes have been associated with hypertension, OH, and orthostatic intolerance. However, few data are available on the genetic predisposition for OHT.

Therefore, we hypothesized that polymorphisms of β_1/β_2*-AR* may contribute to OH or OHT in hypertensive patients. To test our hypothesis, we investigated the association of orthostatic BP dysregulation with two

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Manuscript received: November 19, 2013; **revised:** December 18, 2013; **accepted:** December 28, 2013
DOI: 10.1111/jch.12272

common polymorphisms of β_1/β_2-*AR* genes in 3630 untreated hypertensive patients and 826 normotensive patients.

METHODS

Study Population

The study population was from a community-based cross-sectional study conducted in XinYang County, a middle region in China, from 2004 to 2005. Details of patient recruitment have been previously described.[17] Briefly, a multistage cluster sampling method was used to select a representative sample of rural community residents, aged 40 to 75 years. Hypertension was defined as diastolic BP ≥90 mm Hg and/or systolic BP ≥140 mm Hg or currently taking medication for hypertension. Patients were excluded from the study if they had any known diseases, including heart failure, renal failure, valvular heart disease, secondary hypertension, or severe debilitating chronic illness (cancer or renal or hepatic diseases). To exclude the effect of antihypertensive drugs on orthostatic BP regulation, only untreated patients were included in the study. Untreated patients were defined as those with newly diagnosed hypertension and/or not receiving any antihypertensive drugs for at least 8 weeks. Except for alcohol drinking, no other medications or herbal compounds for comorbidities were recorded within 8 weeks before the study. Although >80% women were postmenopausal, hormonal replacements were not available for them, including estrogens. Concurrently, age- and sex-matched patients with systolic and diastolic BP levels <130/85 mm Hg and with no family history of hypertension were recruited as normotensive patients from the same communities. In total, 3630 untreated patients and 826 normotensive patients with orthostatic BP measurements were included in the study. This study conformed to the ethical guidelines of the 1964 Declaration of Helsinki and was reviewed and approved by the ethical committees of FuWai and local hospitals, and informed consent was obtained from each patient before enrollment.

Data Collection

Each eligible participant was interviewed in a community clinic. The demographic and following vascular risk factors were recorded: body mass index (BMI), waist-hip ratio, fasting blood glucose, blood lipids (total cholesterol [TC], triglycerides [TGs], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C]), serum uric acid, and creatinine levels. Medical history and cigarette smoking and alcohol consumption were obtained with a standardized questionnaire. All patients underwent standard 12-lead electrocardiography (ECG).

BP Measurement and Classification of Orthostatic BP Change

Sitting BP was measured by trained nurses or physicians with a standardized mercury sphygmomanometer and appropriate cuff sizes (regular, large, or thigh) fitted to the patient's right arm. Three readings were recorded in the sitting position at least 30 seconds apart after more than 5 minutes of rest, and the average of the 3 readings was taken as the analyzed BP level. All BP investigators had to complete a training program on the preparation of study patients for measuring BP, selection of correct cuff size, and standard technique for BP measurement according to a common protocol adapted from procedures recommended by the American Heart Association.[20]

Supine and standing BP measurements were recorded with a mercury sphygmomanometer following a standardized protocol by a trained physician or nurse. After a 15-minute ECG examination with the participant lying on an examination table, 3 supine measurements of BP and heart rates were measured at approximately 30-second intervals by a trained professional. Participants were then asked to stand from the supine position with the entire forearm relaxed and supported at heart level on an adjustable table, and standing measurements were taken at 0 and 2 minutes. OH was defined as a decline in SBP of at least 20 mm Hg and/or a decline in DBP of at least 10 mm Hg after either 0 or 2 minutes from a supine to an upright posture.[1] The definition of OHT was a postural increase of at least 20 mm Hg in the orthostatic SBP change.[2] Participants with neither of these two patterns were classified into an orthostatic normotension (ONT) group. The orthostatic BP change was calculated from the average of two standing BP readings minus the average of supine BP readings.

Polymorphisms Selection and Genotyping

β_1- and β_2-*ARs* are key components in SNS. The polymorphisms of β_1-*AR* Arg389/Gly (rs1801253) and β_2-*AR* Arg16/Gly (rs1042713) were selected because of their association with OH and responses to postural change in previous studies.[21,22] These two polymorphisms were detected by standard polymerase chain reaction restriction fragment length polymorphism analysis, gel electrophoresis, and ethidium bromide staining. All aspects of DNA source, preparation, and genotyping were controlled using the paradigms of blindness and randomization. The reproducibility of the genotyping was confirmed by bidirectional sequencing in 100 randomly selected samples, and the reproducibility was 100%. The sequences of all primers and conditions for amplification are listed in Table S1.

Statistical Analysis

All of the data were analyzed with SPSS statistical software (version 15.0; SPSS Inc, Chicago, IL, USA). Quantitative variables were compared with one-way analysis of variance (ANOVA), and Tukey's test or *t*-test was used for comparison of the mean values for pairs of groups. The TG level was highly skewed and was compared using a Mann-Whitney nonparametric test. A χ^2 test was used for qualitative variables and for the Hardy-Weinberg equilibrium of polymorphisms.

Multivariate logistic regression analysis was used to assess the contribution of genotypes to OHT or OH with adjustment for age, BMI, sitting BP levels, heart rates, LDL-C, and fasting blood glucose. The orthostatic BP changes among genotypes were compared first by ANOVA or *t*-test, and then by a general linear model with adjustment for age, BMI, and sitting BP levels. After Bonferroni correction, a two-tailed *P* value of <.025 (.05/2) was considered statistically significant.

RESULTS

Clinical Characteristics, Prevalence of OHT and OH, and Orthostatic BP Changes

Table I summarizes most baseline characteristics, the prevalence of OHT and OH, and orthostatic BP changes in hypertensive and normotensive patients. As expected, SBP, DBP, and most of the other characteristics were higher in hypertensive patients than in normotensive patients. Hypertensive patients had a higher prevalence of OH and OHT (15.7% vs 8.6% and 23.2% vs 15.1%; all *P*<.001) than normotensive patients.

Polymorphisms in Hypertensive and Normotensive Patients

The genotype/allele frequencies of the *β1-AR* Arg389/Gly and *β2-AR* Arg16/Gly in 3630 untreated hypertensive patients and 826 normotensive patients are listed in Table S2. The testing of Hardy-Weinberg equilibrium for two single-nucleotide polymorphisms showed no significant deviation in normotensive patients (rs1801253: χ^2=2.99, *P*=.08; rs1042713: χ^2=0.07, *P*=.79). The distribution of each genotype was consistent with other published data on Chinese patients.[23,24] Because this study focused on the role of *β1-AR* Arg389/Gly and *β2-AR* Arg16/Gly in orthostatic BP dyregulation, the sample size of normotensive patients was not matched with hypertensive patients and no association between the two studied polymorphisms and hypertension risk was found under three genetic models (Table S2).

Associations of Polymorphisms With OH and OHT in Hypertensive and Normotensive Patients

The distribution of genotypes among untreated hypertensive patients with OH, OHT, or ONT is listed in Table II. Because it is controversial whether a sex difference exists in the BP response to standing,[25,26] all of the data for each sex were analyzed separately. The frequency of Arg389/Gly GG genotype of β_1-AR were significantly higher in OH patients (8.4% vs 4.2%, *P*<.0001) and lower in OHT patients (1.4% vs 4.2%, *P*=.002) as compared with ONT patients under the recessive model. When data were analyzed separately by sex, the frequency of *β1-AR* Arg389/Gly GG genotype was only found to be significantly higher in female OH patients (9.1% vs 4.0%, *P*<.0001) but not in male patients (7.1% vs 4.7%, *P*=.146). In contrast, the frequency of GG genotype was only found to be significantly lower in male OHT patients (1.0% vs 4.7%, *P*=.017), but not in female patients (1.7% vs 4.0%, *P*=.033). The *β2-AR* Arg16/Gly GG genotype was slightly more common in OH patients compared with ONT patients (22.7% vs 19%, *P*=.024) under the recessive model. However, no significant associations between *β2-AR* Arg16/Gly and OH or OHT were found when data were analyzed separately by sex (Table II).

TABLE I. Clinical Characteristics and Prevalence of OH and OHT

Characteristics	Untreated Hypertensive Patients	Normotensive Controls
No.	3630	826
Age, y	57.9±8.7[a]	54.4±8.9
BMI, kg/m^2	26.0±3.5[a]	24.1±3.3
SBP, mm Hg	163±21[a]	126±11
DBP, mm Hg	97±12[a]	82±8
PP, mm Hg	66±18[a]	44±9
HR, beats per min	73±12[a]	71±11
TC, mmol/L	5.51 (5.31–5.68)	5.29 (5.03–5.46)
TG, mmol/L	1.69 (1.54–1.80)	1.51 (1.37–1.73)
eGFR, mL/(min·1.73 m^2)	102.8±29.6[a]	108.1±27.1
Serum chloridion, mmol/L	107.7±4.4	107.4±3.5
Serum potassium, mmol/L	4.5±0.8	4.5±0.6
Serum sodium, mmol/L	144.0±5.3	142.9±4.3
Smoking, % (No.)	16.7 (607)[a]	10.7 (88)
Alcohol use, % (No.)	19.5 (709)[a]	12.5 (103)
OHT, % (No.)	15.7 (570)[a]	8.6 (72)
OH, % (No.)	23.2 (849)[a]	15.1 (127)
ΔSBP at 0 min, mm Hg	−3.5 (−4.4 to −2.3)	−3.3 (−4.7 to −1.5)
ΔDBP at 0 min, mm Hg	1.5 (0.9–2.2)	0.3 (−1.0 to 1.7)
ΔSBP at 2 min, mm Hg	−2.1 (−2.7 to 1.2)	−2.8 (−4.0 to 1.8)
ΔDBP at 2 min, mm Hg	3.0 (2.2–3.9)	1.4 (0.2–2.8)
History of dyslipidemia, % (No.)	35.3 (1281)[a]	25.7 (212)
History of DM, % (No.)	8.0 (289)[a]	5.3 (44)
History of stroke, % (No.)	9.6 (347)[a]	2.7 (22)
History of CAD, % (No.)	8.0 (291)[a]	3.0 (25)

Abbreviations: ΔDBP, orthostatic change in diastolic blood pressure; ΔSBP, orthostatic change in systolic blood pressure; BMI, body mass index; CAD, coronary artery disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, heart rate; OH, orthostatic hypotension; OHT, orthostatic hypertension; PP, pulse pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

[a]*P*<.05.

TABLE II. Prevalence of OHT and OH Among Genotypes in Untreated Hypertensive Patients

		Genotype Frequencies, No. (%)			Additive Model	Dominant Model	Recessive Model
		MM	Mm	mm	*P* Value	*P* Value	*P* Value
β*1-AR* Arg389/Gly		CC	CG	GG			
Total	ONT	1304 (59.5)	795 (36.3)	93 (4.2)			
	OHT	339 (61.0)	210 (37.8)	8 (1.4)	.120	.555	**.002**
	OH	438 (52.8)	318 (38.3)	70 (8.4)	**<.001**	**.001**	**<.0001**
Female	ONT	866 (59.5)	531 (36.5)	58 (4.0)			
	OHT	217 (60.4)	137 (38.2)	6 (1.7)	.353	.793	.033
	OH	296 (52.7)	211 (37.5)	51 (9.1)	**<.001**	**.009**	**<.0001**
Male	ONT	438 (59.4)	264 (35.8)	35 (4.7)			
	OHT	122 (61.9)	73 (37.1)	2 (1.0)	.174	.525	**.017**
	OH	142 (53.0)	107 (39.9)	19 (7.1)	.040	.067	.146
β_2-*AR* Arg16/Gly		AA	AG	GG			
Total	ONT	651 (29.8)	1118 (51.2)	414 (19.0)			
	OHT	148 (27.2)	287 (52.7)	110 (20.2)	.239	.221	.518
	OH	230 (28.0)	405 (49.3)	186 (22.7)	.054	.332	**.024**
Female	ONT	460 (31.7)	737 (50.8)	254 (17.5)			
	OHT	101 (28.5)	179 (50.6)	74 (20.9)	.108	.248	.137
	OH	167 (29.9)	274 (49.1)	117 (21.0)	.130	.442	.073
Male	ONT	191 (26.1)	381 (52.0)	160 (21.9)			
	OHT	47 (24.6)	108 (56.5)	36 (18.8)	.784	.676	.365
	OH	63 (24.0)	131 (49.8)	69 (26.2)	.193	.495	.148

Abbreviations: OH, orthostatic hypotension; OHT, orthostatic hypertension; ONT, orthostatic normotension. Bold values indicate significance.

After adjustment for age, BMI, sitting SBP, supine heart rates, LDL-C, and fasting blood glucose by multivariate logistic regression analysis, we found that the β_1-*AR* Arg389/Gly GG genotype conferred about a 3-fold (odds ratio, 3.10; 95% confidence interval, 1.27–7.61) risk of OH in female hypertensive patients. The association of β_1-*AR* GG genotype with OHT disappeared after adjustment for conventional risk factors. And the relationship between the Arg16/Gly GG genotype of β_2-*AR* and OH risk also disappeared after multivariate logistic regression analysis. In addition, as shown in Table III, no association was identified between studied polymorphisms and OHT or OH in normotensive patients, even after adjusting for conventional risk factors (Table III).

Association of Orthostatic BP Changes With Genotypes in Hypertensive and Normotensive Patients

We then analyzed whether there existed a difference in orthostatic BP changes between genotypes after controlling for confounders by using a general linear model with adjustment for age, BMI, and sitting BP levels in both sexes. In female patients, the adjusted orthostatic fall of SBP was 6.5 mm Hg greater in β_1-*AR* 389Gly homozygote carriers than in Arg389 allele carriers (GG-8.9±13 mm Hg vs CC + CG −2.4±12 mm Hg, $P<.001$; Figure), but no significant influence of the β_2-*AR* Arg16/Gly genotypes on the orthostatic SBP or DBP changes was found in female or male hypertensive patients. Also, no association of orthostatic SBP or DBP changes with the studied polymorphisms was found in normotensive patients.

DISCUSSION

The present study assessed the association of β_1/β_2-AR genetic variants with orthostatic BP dysregulation in a large cohort of untreated hypertensive and normotensive patients. In untreated hypertensive patients, we found that the β_1-*AR* Arg389/Gly polymorphism was associated with both OH and OHT while the β_2-*AR* Arg16/Gly polymorphism was only associated with OH after Bonferroni correction. When data were analyzed separately by sex, β_1-*AR* Arg389/Gly polymorphism was associated with OH in women and with OHT in men. After adjustment for age and other conventional risk factors, we found that the β_1-*AR* Gly389 homozygote conferred about a 3-fold risk of OH, and also independently predicted a 6.5 mm Hg greater orthostatic SBP decrease in female hypertensive patients. In contrast, no association between β_1/β_2-*AR* genetic variants and OH or OHT was found in normotensive patients.

The polymorphism of β_1-*AR* Arg389/Gly has been associated with increased risk of hypertension in past studies.[23,27,28] A recent meta-analysis reported a marginally significant association in Caucasian patients, but no association has been found in Chinese patients.[29] Our finding of no association between β_1-*AR* Arg389/Gly and hypertension was consistent with the results of the meta-analysis, although the present study was not designed to investigate the impact of β_1-*AR* Arg389Gly on hypertension. The racial differences in distribution of β_1-*AR* Arg389/Gly might have an explanation. Further large sample studies are needed to confirm the impact of β_1-*AR* Arg389/Gly on hypertension in Chinese patients.

TABLE III. Prevalence of OHT and OH Among Genotypes in Normotensive Patients

		Genotype Frequencies, No. (%)			Additive Model	Dominant Model	Recessive Model
		MM	Mm	mm	*P* Value	*P* Value	*P* Value
β1-AR Arg389/Gly		CC	CG	GG			
Total	ONT	368 (60.0)	201 (32.8)	44 (7.2)			
	OHT	47 (65.3)	20 (27.8)	5 (6.9)	.39	.39	.94
	OH	75 (60.5)	39 (31.5)	10 (8.1)	.93	.93	.73
Female	ONT	249 (62.1)	126 (31.4)	26 (6.5)			
	OHT	31 (66.0)	13 (27.7)	3 (6.4)	.61	.61	.98
	OH	48 (60.0)	26 (32.5)	6 (7.5)	.72	.73	.74
Male	ONT	119 (56.1)	75 (35.4)	18 (8.5)			
	OHT	16 (64.0)	7 (28.0)	2 (8.0)	.45	.45	.93
	OH	27 (61.4)	13 (29.5)	4 (9.1)	.52	.52	.90
β2-AR Arg16/Gly		AA	AG	GG			
Total	ONT	165 (27.2)	328 (54.0)	114 (18.8)			
	OHT	22 (31.0)	37 (52.1)	12 (16.9)	.50	.50	.70
	OH	38 (30.6)	63 (50.8)	23 (18.5)	.43	.43	.95
Female	ONT	112 (28.0)	212 (53.0)	76 (19.0)			
	OHT	14 (30.4)	24 (52.2)	8 (17.4)	.73	.73	.79
	OH	25 (30.9)	40 (49.4)	16 (19.8)	.60	.60	.88
Male	ONT	53 (25.6)	116 (56.0)	38 (18.4)			
	OHT	8 (32.0)	13 (52.0)	4 (16.0)	.49	.49	.77
	OH	13 (30.2)	23 (53.5)	7 (16.3)	.53	.53	.75

Abbreviations: OH, orthostatic hypotension; OHT, orthostatic hypertension; ONT, orthostatic normotension.

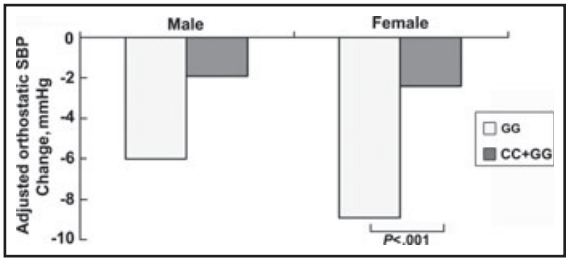

FIGURE. Orthostatic systolic blood pressure (SBP) change based on β1-AR Arg389Gly genotypes after adjustment for age, body mass index, and sitting SBP levels using a general linear model in untreated hypertensive patients. GG indicates Gly389 homozygote; CC+CG, Arg389 alleles.

In hypertensive patients, the orthostatic BP response might be influenced by high BP levels as well as subsequent damage of vessel and autonomic tone. In contrast, OHT may be related to the sympathetic hyperactivity presented in some hypertensive patients.[30] The excessive venous pooling in the lower extremities upon standing can lead to a decrease in cardiac output, which may result in a vigorous activation of SNS and excessive arteriolar vasoconstriction in hypertensive patients with sympathetic hyperactivity and then the presence of OHT.

The genetic influence on orthostatic BP dysregulation (OH or OHT) is not well understood. Because of the principal role of the autonomic nervous system in both the short- and long-term response to postural changes,[31] Tabara and colleagues[21] reported the association of OH with the G protein α subunit (*GNAS1*) T131C and G protein β subunit (*GNB3*) C825T polymorphisms, which indicate that genes encoding sympathetic nervous components may be involved in the predisposition for OH. *β1-AR* expressed in the heart mediates the actions of catecholamines of the SNS by interacting with the G protein. One study has shown that the *β1-AR* Gly49 polymorphism is protective for idiopathic orthostatic intolerance, but no association was found for the β_1-AR Arg389Gly polymorphism, which may be the result of the small sample size.[32] The *β1-AR* Arg389Gly polymorphism is located within a predicted fourth intracellular loop, an important region for receptor coupling to intracellular signaling molecules. Accumulated data indicate that the Arg389 *β1-AR* is more efficient at stimulating adenylyl cyclase and exhibits increased signaling as compared with the Gly389 *β1-AR*.[33,34] Our results of the associations between *β1-AR* Gly389 homozygote with OH and OHT were consistent with the depressed function of Gly389 β_1-AR. The response of SNS activation to postural change might be dull in *β1-AR* Gly389 homozygote carriers, with the risk of OH increased while the occurrence of OHT decreased in *β1-AR* Gly389 homozygote carriers. Because no sex differences in genotypes distribution was found in both hypertensive and normotensive patients in our study, the sex differences in the association between *β1-AR* Arg389/Gly and OH or OHT was speculated to be associated with possible sex differences in response to *β-AR* stimulation.[35] We do not have an answer for why the polymorphism (*β1-AR* Gly389) applies only to

women. Human studies reveal sex differences in myocardial function as well as in the incidence and manifestation of heart disease. The differences in both human and animal heart pathology are connected with estrogen levels.[36–38] Sex differences in the patients with *AR* polymorphism have been identified in both human and animal studies. Polymorphisms in the β_1-*AR* and β_3-*AR* have been associated with an increase in cardiovascular risk in women.[39] A protective association was found between the Gly16-Gln27-Ile164 haplotype and myocardial infarction among men by using a haplotype-based analysis,[40] but did not find a single-marker or haplotype association between three functionally relevant polymorphisms in the *ADRB2* gene and incident myocardial infarction, ischemic stroke, or death caused by cardiovascular disease in a large study of more than 25,000 women.[41] In an animal study, female mice had significantly less cardiac remodeling, dysfunction, and pathology and a marked survival advantage over male mice in an animal model of cardiac β_2-*AR* overexpression–induced cardiomyopathy and heart failure with aging.[42] In intact animals, resting heart rate has been found to be significantly less in Ile-164 mice than in wild-type β_2-*AR* mice.[43] An association between *ADRB2* gene variation Arg16/Gly and postural hemodynamics has also been found in a young healthy population.[22] This may have implications in the development of orthostatic disorders.

The association of β_1-*AR* Gly389 homozygote with OHT and the relationship between β_2-*AR* Arg16/Gly and OH risk disappeared after adjustment for conventional risk factors. Therefore, further studies are needed to determine the role of studied polymorphisms in orthostatic BP regulation in both men and women. In normotensive patients, no association was found between two β_1/β_2-*AR* polymorphisms and OH or OHT. Hypertension has been associated with increased risk of OHT and OH.[44,45] Together, with no differences of β_1/β_2-*AR* polymorphisms between hypertensive and normotensive patients, our results indicate that the impact of β_1-*AR* Arg389Gly polymorphism on OH might be predominant in hypertensive patients. The exact mechanism needs to be elucidated experimentally in the future.

STUDY LIMITATIONS AND STRENGTHS

Several limitations need to be mentioned. First, we did not replicate our results in another independent sample of hypertensive patients because the study sample size was large enough to have >80% statistical power to detect an association (at P=.05) with an odds ratio of 1.25 to 1.75 for alleles at 35% to 45% frequency. Also, Bonferroni correction decreased the possibility of a false-positive result. Second, it might be helpful to investigate all polymorphisms in all genes encoding pathways of the SNS to further evaluate the genetic background of orthostatic BP dysregulation. However, more candidate genetic polymorphisms need to be analyzed in a larger sample cohort with higher prevalence of OH or OHT. Another limitation is the lacking description of heart rate during postural change in our study. In fact, we concurrently recorded a slight increase in heart rate (5–10 beats per minute) with a fall in BP upon arising within 1 minute, but the heart rate returned to the basic supine level after 2 minutes of standing. There are some method limitations to our heart rate monitoring. Heart rate was acquired intermittently together with BP measurement when using mercury column sphygmomanometry, not with continuous ECG heart rate monitoring, due to the large quantity of sample. This may introduce systemic error. Another explanation was that the arterial stiffness, aging, as well as hypertension may impair baroreflex sensitivity and contribute to orthostatic BP change.[46–49] Failure in heart rate response to postural change may also be caused by autonomic insufficiency, but autonomic functions were not tested in this study. Despite these limitations, our results in normotensive patients verified the reliability of our findings. Also, all participants were recruited from the same geographic area and had similar dietary style (including salt intake). This community-based approach helped to avoid population stratification and minimize the influence resulting from variations in lifestyles from different areas in China.

CONCLUSIONS

Our results provide evidence for the involvement of β_1-*AR* in the genetic predisposition to orthostatic BP dysregulation in hypertensive patients, but not in normotensive patients.

Acknowledgments: We appreciate the cooperation of the patients and many investigators in the FuWai, Beijing Center and local clinical centers in XinYang, Henan Province. This work was supported by grant (30871054) from National Natural Science Foundation of China to Dr Fan Xiaohan and government funding from the National Twelfth Five-Year Project to Dr Hui Rutai (2011BAI11B04).

Conflict of Interest: The authors declare that they have no conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. The sequences of all primers and conditions for amplification.

Table S2. Studied genotypes in untreated hypertensive patients and normotensive patients.