Associations between CYP2D6*10 and ADRB1(1165G > C) gene polymorphisms and the response to metoprolol therapy in essential hypertension

Abstract

Objective: To investigate whether CYP2D6*10 and ADRB1 (1165G > C) gene polymorphisms are associated with the risk of EH and metoprolol clinical response to the Han Chinese patients in Huaihai region. **Methods:** All patients with EH were hospitalized in the Affiliated Hospital of Xuzhou Medical University from January 2018 to June 2020, while healthy subjects were recruited from the health examination center of the Affiliated Hospital of Xuzhou Medical University. Gene polymorphisms of CYP2D6*10 and ADRB1 (1165G > C) were identified by gene chip method. A total of 980 patients with EH and 250 healthy controls were successfully classified. 217 EH patients carrying different CYP2D6*10 and ADRB1 (1165G > C) genotypes orally took metoprolol extended release tablet 47.5 mg daily for 15 consecutive days. Low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), total cholesterol (TC), triglycerides (TG), and fasting blood glucose (GLU) were obtained from patients with EH and healthy controls. **Results:** The genotype and allele distributions of the CYP2D6*10 and ADRB1 (1165G > C) polymorphisms were consistent with the Hardy-Weinberg equilibrium ($P > 0.05$). There were no significant differences in genotypic and allelic frequencies of CYP2D6*10 and ADRB1 (1165G > C) between the EH group and the healthy controls ($P>0.05$), indicating that these two polymorphisms do not increase the risk of developing EH. The basic clinical characteristics of BMI, GLU, LDLC, HDLC, baseline SBP and baseline DBP were significantly different between the patients with EH and healthy controls in ($p < 0.05$). After adjusting for confounding factors, we found that there was no relationship between CYP2D6*10 gene polymorphism and the decrease of SBP and DBP in all subjects after 15 days of metoprolol therapy. The same results were also obtained in the

male and female subgroups. However, the ADRB1 (1165G > C) homozygous carriers in the female subgroup had stronger antihypertensive effects than the heterozygous carriers (P=0.04 for SBP and P=0.02 for DBP) after adjusting confounding factors by multiple linear regression, while there was no difference in male subgroup. The ADRB1(1165G > C) genotype of patients should be considered when taking metoprolol for hypertension，especially in female. **Conclusions:** The results indicate that CYP2D6*10 and ADRB1 (1165G > C) gene polymorphisms are not associated with the susceptibility to essential hypertension. ADRB1 (1165G > C) polymorphism is a major factor affecting the antihypertensive effect of metoprolol and personalized therapy should be performed according to patient genotype among female.

Keywords: CYP2D6, ADRB1, hypertension, metoprolol, polymorphism

Introduction

At present, more than one-third of adults worldwide suffer from hypertension, and this number is expected to increase to 1.56 billion by 2025[1], in which essential hypertension (EH) accounts for about 90%. Hypertension is one of the primary risk factors for cardiovascular diseases, stroke and renal failure, so controlling blood pressure can reduce the risk of these diseases. EH is defined as an elevated blood pressure (BP) without an identifiable cause and is considered to be influenced by a combination of environmental and genetic factors. Although it is easy to describe the environmental factors that are susceptible to EH, the vast majority of subjects still do not know the genetic components that increase this susceptibility.

As per current evidence, genetic factors are estimated to account for approximately 30-50% of variation in blood pressure levels[2]. It is indicated that genetic variations may influence the clinical response to antihypertensive agents in recent studies. Because of individual genetic differences, there are large differences among patients in the way they respond to antihypertensive drugs, this also causes the blood pressure compliance rate of patients to be suboptimal despite taking the drugs. A study conducted in the suburban town of Shanghai demonstrated that the prevalence of EH among elderly patients (aged ≥60 years) in China was 59.4%, but only 24.4% of patients with EH have their blood pressure effectively controlled[3], so, how to achieve the best effect of antihypertensive drugs in different patients has become an increasingly important medical and public health issue[4].

Metoprolol is a cardioselective β-1 adrenergic receptor (ADRB1) blocker, which is widely used in the treatment of various cardiovascular diseases because it can reduce the mortality of patients[5]. It regulates the sympathetic response by blocking human β-1 adrenergic receptor and plays an important role in the management of EH. There are obvious individual differences in the antihypertensive effect of metoprolol, and many factors contribute to this phenomenon, among which genetic polymorphism may be the most important one. There is evidence that ADRB1 and CYP2D6 variants play key roles in interpreting individual differences in metoprolol clinical efficacy[6,7], so,

genetic testing of ADRB1 and CYD2D6 prior to the application of metoprolol may have a predictive effect on the antihypertensive effect among different individuals.

ADRB1 is encoded by an intronless gene of 477 amino acids on chromosome 10q25.3. It is a member of seven transmembrane G-protein coupled receptor families that plays an important physiological role in the heart, blood vessels, respiratory, metabolic, endocrine and central nervous system. There are many mutations in ADRB1, and previous studies on the ADRB1 polymorphism have focused on the Ser49Gly and Arg389Gly (1165G > C) polymorphisms[8]. In a large meta-analysis of over 86 000 people from the general population, the 1165G polymorphism was associated with an increased risk of hypertension[9]. Many studies have also reported that 1165G polymorphism was linked to a significant reduction in response to β-blockers[10,11].

The cytochrome P450 enzyme (CYP450) system has an important role in the biotransformation of many endogenous and exogenous substances including drugs, food additives, and pollutants. The CYP2D6 gene, located on chromosome 22 (locus 22q13.1), is a polypeptide of 497 amino acids. CYP2D6 accounts for less than 2% of the whole CYP450 family, but it plays an important role in drug metabolism, about 25% of all drugs in clinical are metabolized by CYP2D6[12]. In East Asian populations including China, the most common mutation in CYP2D6 is CYP2D6*10, with a mutation frequency of 67.9%[13]. Several studies have identified an influence of CYP2D6*10 polymorphisms on metoprolol metabolism rate[14,15]. However, some other studies have shown that there is little or no connection between the CYP2D6*10 polymorphism and metoprolol efficacy[16,17].

Although there is some evidence that ADRB1(1165G > C) and CYP2D6*10 gene polymorphisms influence the response to antihypertensive therapy with β-blockers, there is ongoing debate concerning the clinical importance of these effects. The purpose of our study, therefore, was to determine whether CYP2D6*10 and ADRB1 (1165G > C) gene polymorphisms are associated with the risk of EH and the metoprolol clinical response to the Han Chinese patients in Huaihai region with EH.

Materials and methods

Selection of study population

All patients with EH were hospitalized in the Affiliated Hospital of Xuzhou Medical University from January 2018 to June 2020, while healthy subjects were recruited from the health examination center of the Affiliated Hospital of Xuzhou Medical University. EH patients and healthy controls were all from Han nationality in Huaihai region of China. The inclusion criteria for all subjects were Han Chinese origin, a body mass index (BMI) of 18.5–30 kg/m^2, aged between 18 and 80 years, 140 mm Hg≤systolic blood pressure (SBP) <180 mm Hg and/or 90 mm Hg≤diastolic blood pressure (DBP) <110 mm Hg, having never received antihypertensive therapy or discontinued from antihypertensive therapy for at least 4 weeks before recruitment. Healthy controls and EH patients came from the same area and were similar to their age and gender. They had no hypertension (90 mm Hg < SBP < 140 mm Hg and 60 mm Hg < DBP < 90 mm Hg). Patients with a history of chronic cardiovascular and cerebrovascular disease, chronic liver and kidney disease, bradycardia and congestive heart failure were excluded from the study. Patients with secondary hypertension, pregnancy, lactation or receiving other drugs that may affect blood pressure or the efficacy of metoprolol were also excluded.

A total of 980 patients with EH (608 male and 372 female) and 250 healthy controls (152 male and 98 female) were enrolled for the analysis of CYP2D6*10 and ADRB1(1165G > C) polymorphisms. Between 7:00 and 8:00 in the morning, a trained nurse selected a mercury column sphygmomanometer with a suitable size cuff to measure the SBP and DBP of the subjects. Subjects should rest for at least 5 minutes in a quiet manner, and smoking, coffee or tea should not be allowed for 30 minutes before the measurement. SBP and DBP were measured every 5 minutes for a total of 3 times and the average of the last two measurements was recorded. After 15 days, the resting blood pressure of subjects in metoprolol group was measured by the same person with the same sphygmomanometer at the same time.

Each participant was interviewed using a standardized questionnaire to pick up the information on gender, age, height and weight. BMI was calculated as weight in

kilograms divided by the square of height in meters. The peripheral venous blood of patients were collected to obtain laboratory indicators, such as low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), total cholesterol (TC), triglycerides (TG), and fasting blood glucose (GLU). All subjects were instructed to maintain an empty stomach over a 12 h prior to blood sampling in the morning.

Among the 980 patients with EH in the study, 217 patients with EH (136 male and 81 female) carrying different CYP2D6*10 and ADRB1 (1165G > C) genotypes orally took metoprolol extended release tablet 47.5 mg daily for 15 consecutive days. To control the effects of other gene polymorphisms, these 217 EH patients carried the same *1*1 genotype of CYP2C9*3 and 1166AA genotype of angiotensin II receptor 1 (AGTR1). The study was performed in accordance with the Helsinki Declaration, and the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University approved the protocol. Written informed consent was obtained from each subject prior to the study.

Genotyping

The genotypes of subjects including CYP2D6*10, ADRB1 (1165G > C), CYP2C9*3 and AGTR1 (1166A>C) were identified by gene chip method. The steps are as follows: freshly drawn peripheral venous blood (2 ml) was collected into tubes containing EDTA under fasting conditions. Genomic DNA was extracted by using a TIANGEN Blood DNA extraction kit (Tiangen, Beijing, China) and then stored at 4 °C until use. Single-nucleotide polymorphism (SNP) genotyping was performed according to the manufacturer's protocols. The PCR amplification conditions included an initial denaturation at 95 °C for 5 min, followed by 40 cycles with denaturation at 95 °C for 40 s, annealing at 60 °C for 40 s and extension at 72 °C for 40 s, followed by a final extension step at 72 °C for 5 min. The products of PCR were hybridized and then sequenced on a Genepix 4100A Biochip Scanner (Molecular Devices, Sunnyvale, USA).

Statistical analysis

The data were statistically analyzed with the SPSS 21.0 software package (SPSS,

Chicago, USA). Continuous variables were summarized as mean ± SD, and categorical variables were summarized as values. Hardy-Weinberg equilibrium was assessed by chi-square (χ^2) test. Allele frequencies were calculated from the genotypes of all patients. The χ^2 test or Fisher exact test was used for categorical variables. Mean comparison between the two groups was analyzed by the t-test, and multiple group means were compared by one-way ANOVA. Multivariate linear regression analysis was carried out to estimate the association of different genotypes and BP reduction, adjusting for age, gender, BMI, LDLC, HDLC, TC, TG，GLU and baseline BP. The efficacy of metoprolol was defined as the change of SBP and DBP before and after the treatment with metoprolol for 15 days. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Clinical and biochemical characteristics of subjects

Samples from 980 patients with EH and 250 healthy controls were used to determine genotypes with regard to the CYP2D6*10 and ADRB1 (1165G > C) polymorphisms. The basic clinical characteristics of the subjects were presented in Table 1. There were significant differences between the patients with EH and healthy controls in weight, BMI, GLU, LDLC, HDLC, baseline SBP, baseline DBP ($p < 0.05$ for each).

Table 1 Clinical characteristics of patients with EH and healthy controls.

Parameter	Healthy controls (n =250)	Patients with EH (n = 980)	P value
Sex (male/female)	152/98	608/372	0.723
Age (years)	60.42±13.46	60.97±13.92	0.576
Height（cm）	165.93±7.65	166.64±8.16	0.239
Weight（kg）	69.10±11.63	71.75±14.26	0.010
BMI (kg/m^2)	25.03±3.32	25.72±3.95	0.015
GLU (mmol/L)	5.96±2.11	6.12±2.09	0.016

TG (mmol/l)	5.02±1.21	5.06±1.29	0.337
TC (mmol/l)	1.70±1.27	1.81±1.80	0.052
HDLC (mmol/l)	1.29±0.39	1.24±0.38	0.001
LDLC (mmol/l)	2.88±0.97	2.97±1.03	0.009
Baseline SBP (mm Hg)	121.34±17.83	163.20±20.02	0.000
Baseline DBP (mm Hg)	70.67±8.28	95.42±13.17	0.001

Abbreviations: EH, essential hypertension; BMI, body mass index; GLU, fasting blood glucose; TG, triglycerides; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Data are given as mean ± SD.

Genotypic and allelic frequencies analysis

The genotypic and allelic frequencies of the CYP2D6*10 and ADRB1(1165G > C) polymorphism in patients with EH and healthy controls were shown in Table 2. The genotype and allele distributions of the two polymorphisms were consistent with the Hardy-Weinberg equilibrium (P > 0.05 for each，data not shown), indicating that the subjects in our study were representative of the population. There were no significant differences between EH patients and healthy controls in the genotype and allele distributions in the two polymorphisms, which suggested that these two polymorphisms do not increase the risk of developing EH.

Table 2 Genotypic and allelic frequencies of CYP2D6 *10 and ADRB1(1165G＞C) polymorphism in patients with EH (n=980) and healthy controls (n=250).

Genotypes	Controls n（%）	Patients n（%）	P value
CYP2D6 *10			
*1/*1	45（18）	208（21.22）	0.530
*1/*10	130（52）	502（51.22）	
*10*10	75（30）	270（27.56）	
Alleles			
*1	220（44）	918（46.84）	0.26
*10	280（56）	1042（53.16）	
ADRB1(1165G＞C)			
G/G	18（7.2）	78（7.96）	0.845
G/C	98（39.2）	375（38.27）	
C/C	134（53.6）	527（53.77）	

Alleles			
G	134（26.8）	531（27.09）	0.896
C	366（73.2）	1429（72.91）	

Abbreviations: EH, essential hypertension; CYP2D6，CytochromeP4502D6；ADRB1：beta-1 adrenergic receptor. The genotypic and allelic frequencies are indicated in absolute values (percentage). P values are determined by Pearson's χ^2 test.

Effect of CYP2D6*10 polymorphism on the efficacy of metoprolol in EH patients

Total 217 patients with EH (136 male and 81 female) were chosen to receive metoprolol extended release tablet 47.5 mg daily for 15 consecutive days. The baseline clinical characteristics of the 217 patients were listed in Table 3. Among the different genotypic groups there were no difference in sex distribution, age, height, weight, BMI, GLU, TG, TC, HDLC and LDLC.

Table 3 Baseline characteristics of patients with EH with different CYP2D6 *10 genotypes before treatment with metoprolol.

Parameter	*1/*1(n=46)	*1/*10(n=121)	*10/*10(n=50)	P value
Sex (male/female)	29/17	74/47	33/17	0.836
Age (years)	60.35±12.78	58.44±15.51	57.62±14.03	0.641
Height（cm）	166.80±7.94	166.76±9.36	166.52±8.19	0.984
Weight（kg）	73.86±11.69	72.54±13.93	73.64±16.49	0.435
BMI (kg/m^2)	26.53±3.63	25.95±3.63	27.20±6.78	0.251
GLU (mmol/L)	6.12±1.89	6.11±2.04	5.75±1.78	0.512
TG (mmol/l)	4.68±1.42	4.67±1.04	4.72±1.19	0.963
TC (mmol/l)	1.80±1.08	1.75±1.10	1.69±0.86	0.859
HDLC (mmol/l)	1.24±0.34	1.24±0.34	1.21±0.36	0.871
LDLC (mmol/l)	2.62±1.03	2.63±0.80	2.67±0.80	0.942

Abbreviations: CYP2D6，CytochromeP4502D6； BMI, body mass index; GLU, fasting blood glucose; TG, triglycerides; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol. Data are given as mean ± SD.

Table 4 showed the SBP and DBP of the 217 EH patients with different

CYP2D6*10 genotypes before and after the metoprolol treatment. To our surprise, we could not find difference among the three genotypic groups in SBP and DBP both before and after metoprolol treatment. There was no significant difference in the changes of SBP and DBP among the three groups of patients with different genotypes, either. Stratified by gender, the changes of SBP and DBP were similar among the three genotypes in both male and female (data not shown). After adjusting for confounding factors, multiple linear regression did not reveal a relationship between CYP2D6*10 gene polymorphism and the decrease of SBP and DBP in all subjects, the same results also appeared in the male and female subgroups (data not shown). Our results suggest that CYP2D6*10 gene polymorphism is not associated with the antihypertensive effect of metoprolol.

Table 4 15-days SBP and DBP changes by metoprolol treatment in different CYP2D6 *10 genotypes.

Parameter	*1/*1(n=46)	*1/*10(n=121)	*10/*10(n=50)	P value
Baseline SBP (mm Hg)	163.33±22.26	165.36±20.98	160.36±19.96	0.364
SBP at 15th day(mm Hg)	130.67±15.25	129.15±14.31	129.66±13.82	0.829
SBP Reduction(mm Hg)	32.65±18.80	36.21±19.92	30.70±15.67	0.182
Baseline DBP (mm Hg)	96.17±17.34	96.10±13.28	94.30±14.19	0.736
DBP at 15th day(mm Hg)	73.59±9.89	73.63±11.05	73.48±14.49	0.997
DBP Reduction(mm Hg)	22.59±13.56	22.47±10.99	20.82±11.14	0.667

Abbreviations: CYP2D6，CytochromeP4502D6; SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are given as mean ± SD.

Effect of ADRB1 (1165G > C) polymorphism on the efficacy of metoprolol in EH patients

When compare the baseline clinical characteristics of the 217 EH patients with different ADRB1 (1165 G>C) polymorphisms, we also did not find difference in sex distribution, age, height, weight, BMI, GLU, TG, TC, HDLC and LDLC among the different genotypic groups ($p > 0.05$ for each, data not shown).

We did not find difference among the three ADRB1 (1165G > C) genotypic groups in baseline SBP , baseline DBP, SBP at 15th day, and DBP at 15th day and the changes of SBP and DBP（data not shown), which was similar to the results of CYP2D6*10 polymorphism. After grouped by gender, there were statistical differences between

ADRB1 (1165G > C) polymorphism and BP reduction in female, the results were shown in Table 5, while no difference was found in male（data not shown). In female, we found that the changes of SBP and DBP were different among the three ADRB1 (1165G > C) genotypic groups (P = 0.027 and 0.001, respectively). The GG genotype carriers had the highest blood pressure reduction, followed by CC genotype carriers, while the lowest BP reduction was emerged in GC genotype carriers. A superior efficacy of metoprolol was found in homozygous patients for the ADRB1 (1165G > C) mutant genotype.

Table 5 15-days SBP and DBP changes by metoprolol treatment with different ADRB1(1165G＞C) genotypes in female.

Parameter	GG(n=5)	GC(n=25)	CC(n=51)	P value
Baseline SBP (mm Hg)	167.00±21.76	157.64±18.99	163.12±21.51	0.180
SBP at 15th day(mm Hg)	123.40±11.26	128.72±13.62	126.43±14.87	0.687
SBP Reduction(mm Hg)	42.61±21.35	28.92±15.79	36.69±19.59	0.027
Baseline DBP (mm Hg)	99.20±12.68	89.97±11.70	94.23±12.26	0.157
DBP at 15th day(mm Hg)	71.60±8.05	71.76±7.94	70.67±10.77	0.895
DBP Reduction(mm Hg)	27.60±7.50	14.28±7.94	23.45±10.75	0.001

Abbreviations: ADRB1：beta-1 adrenergic receptor, SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are given as mean ± SD.

We took GG and GC as a whole in female because the GG genotype frequency was too low (6.12%), while the GG genotype frequency in male was 13.2%. The comparison results of the two groups were shown in Table 6. We found the CC genotype carries had a larger DBP reduction and SBP reduction. However, only the DBP reduction reached statistical difference while there was no statistical significance in the SBP reduction.

After adjusting for confounding factors by multiple linear regression, we found that the ADRB1 (1165G > C) homozygous carriers in the female subgroup had stronger antihypertensive effects than the heterozygous carriers (P=0.04 for SBP and P=0.02 for DBP). Although this trend was also observed in all subjects and male subgroups, there was no statistical difference.

Table 6 15-days SBP and DBP changes by metoprolol treatment between ADRB1 (1165G＞C) GG+GC and CC carriers in female.

Parameter	GC+GG(n=25)	CC(n=51)	P value
Baseline SBP (mm Hg)	160.70±20.30	163.12±21.51	0.180

SBP at 15th day(mm Hg)	127.83±13.23	126.43±14.87	0.687
SBP Reduction(mm Hg)	32.87±18.70	36.69±19.59	0.392
Baseline DBP (mm Hg)	90.23±9.21	94.23±12.26	0.248
DBP at 15th day(mm Hg)	71.73±7.82	70.67±10.77	0.895
DBP Reduction(mm Hg)	18.50±9.25	23.45±10.75	0.004

Abbreviations: ADRB1：beta-1 adrenergic receptor, SBP, systolic blood pressure; DBP, diastolic blood pressure. Data are given as mean ± SD.

Discussion

EH is difficult to treat successfully due to individual susceptibility. In this study, the frequency of CYP2D6*10 and ADRB1 (1165G > C) polymorphisms in EH patients and healthy controls were determined, and no significant difference was found between the two groups. So far, there have been few studies on susceptibility to CYP2D6*10 and EH, but there are many different conclusions about the relationship between ADRB1 (1165G > C) and EH. Consistent with our results, Varsha Varakantham et al. did not find a relationship between the 1165G > C gene polymorphism and the prevalence of EH in a study involving 292 patients with EH and 324 healthy controls[18]. Different results were confirmed in other studies. Chen et al. found that ADRB1 1165CC polymorphism was an independent risk factor for EH in Fujian Han subjects[19] after multivariate logistic regression model analysis. In contrast, a meta-analysis by Kitsios et al. found that the risk of EH in the G allele carriers was reduced by 16% compared with the C allele carriers, but this result was not statistically significant[20].

With regards to drug response, there are several factors affect the therapeutic effect of EH patients, the most important factor of which is genetic variation. Currently, as high as 60% of EH patients receive inappropriate antihypertensive therapy, which may be due to individual differences caused by genetic factors[21]. For metoprolol, due to the genetic variations of the drug metabolizing enzyme (CYP2D6) and the ADRB1 polymorphisms, it has greater pharmacokinetic and pharmacodynamic variations.

CYP2D6 is one of the most important CYP enzymes in humans and it is the predominant metabolizing enzyme of metoprolol, about 70% - 80% of the drug is metabolized by CYP2D6. After 15 days of metoprolol therapy, our findings suggested that there is no relationship between CYP2D6*10 polymorphism and the clinical

antihypertensive efficacy of metoprolol, which was in agreement with previous studies[7,22]. CYP2D6*10 polymorphism may have no effect on the response to metoprolol antihypertensive therapy. Although in some studies CYP2D6*10 polymorphism has been confirmed to influence the metabolism of metoprolol[14,15], inconsistent findings have been reported with regard to the influence of this polymorphism on the response to metoprolol therapy[7]. This may be caused by the difference of races, research methods, duration of study, dosage of administration and environmental factors.

The β-blockers play an important role in the treatment of EH, and are widely used for the management of cardiovascular diseases. However, the response to β-blockers varies from individual to individual, which may be due in part to the ADRB1 gene polymorphisms. Vitro studies have shown that EH patients who carried homozygous ADRB1 1165GG variant were more sensitive to β-blockers than those carrying the 1165C allele[23,24]. Multiple studies have demonstrated the influence of ADRB1 polymorphisms on the response to treatment with β-blockers. There is a clear association between ADRB1 (1165G > C) polymorphism and antihypertensive response to metoprolol[25,26]. The present study showed that the ADRB1 (1165G > C) mutation had a significant clinical effect on metoprolol therapy in female. This is consistent with reports that women demonstrated greater β-adrenergic receptor responsiveness than men[27,28]. Data from this study suggested that homozygous genotype of ADRB1 (1165 G > C) is associated with increased efficacy of metoprolol in female with EH, especially the 1165GG genotype. Other studies have revealed an association between ADRB1 1165GG genotype and lower SBP and/or DBP[29,30], which were consistent with our findings. However, we only found the association in female, not in male. We considered the 1165GG genotype and the 1165GC genotype as a whole because of the lower frequency of the 1165GG genotype in female. The 1165CC carriers had a higher SBP and DBP reduction, however, only DBP reduction was related to the ADRB1 (1165 G > C) polymorphism while SBP reduction was irrelevant.

In this study, the ADRB1 (1165G > C) polymorphism was found to have a greater

impact on the antihypertensive effect of metoprolol than the CYP2D6*10 polymorphism, in agreement with previous studies[31,32]. However, there are some limitations in our research. First, the sample size in our study was small, especially for women, a larger sample size is needed to examine the relationship between the two genetic polymorphisms and metoprolol efficacy. Second, factors such as smoking, drinking, diet, and exercise were not included in the analysis. Third, the duration of the study is too short, we should extend the time to get more accurate results. Last but not least, many genetic polymorphisms may affect the antihypertensive effect of metoprolol. But in our study, except the CYP2C9*3 and AGTR1 polymorphisms were consistent in all subjects, we only analyzed the association of ADRB1 (1165G > C) and CYP2D6*10 polymorphisms with the antihypertensive effect of metoprolol, and other polymorphisms were not taken into account.

Conclusion

In our study, the CYP2D6 * 10 and ADRB1 (1165G> C) polymorphisms were not associated with the susceptibility of EH in the Han population of Huaihai region. After 15 days of metoprolol therapy, our findings suggest that there is no relationship between CYP2D6*10 polymorphism and the clinical efficacy of metoprolol, neither in male nor female. At the same time, we found statistical differences between ADRB1(1165G > C) polymorphism and BP reduction in female while no difference was found in male. Thus, ADRB1 (1165G > C) polymorphism is a major factor affecting the antihypertensive effect of metoprolol and personalized therapy can be performed according to patient genotype among female, which may effectively improve hypertension therapy.

Conflict of interest

The authors declare no conflict of interest.

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