

Effects of β_1 -adrenergic receptor and CYP2D6 genetic polymorphism on metoprolol pharmacokinetics and pharmacodynamics in antihypertension therapy

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ABSTRACT BACKGROUND: Metoprolol is a selective β_1 -Blocker commonly used in essential hypertension. It is metabolized by CYP2D6. *CYP2D6* *10, which was identified to decrease activity of CYP2D6, is the main variance in Chinese population. β_1 -adrenergic receptor, with Ser49Gly and Gly389Arg polymorphisms, is the target of metoprolol. It was still unknown that whether the CYP2D6 and β_1 -adrenergic receptor had a synergic effect on metoprolol antihypertension therapy. **AIM:** To clarify the genetic polymorphism associated with metoprolol pharmacokinetics and pharmacodynamics in antihypertension therapy. **METHODS:** 125 mild-to-med essential hypertension patients were enrolled in this study. Patients were mono-theraped with metoprolol for 12 weeks. Blood pressure was monitored every 4 weeks. PCR-RFLP method was use to identify *CYP2D6* *10 and β_1 -adrenergic receptor Ser49Gly and Gly389Arg polymorphisms. Plasma metoprolol concentration was measured by HPLC- fluorescence detection. **RESULTS:** Trough blood level (C_0) of metoprolol was associated with *CYP2D6* *10 variance in a gene-dose-effect manner, whereas the extent of blood pressure decrease was not significant different in *CYP2D6* *1 *1, *1 *10 and *CYP2D6* *10 *10 patients. After 12 weeks metoprolol therapy, Gly49 carriers had stronger decrease in systolic and diastolic blood pressure

than that of Ser49 homozygotes. Similarly, subjects homozygous for Arg389 had stronger decrease in blood pressure than that of Gly389 carriers. **CONCLUSION:** *CYP2D6* *10 variance significantly change the pharmacokinetics of metoprolol, and the genetic polymorphisms of β_1 -adrenergic receptor were associated with the pharmacodynamics of metoprolol in antihypertension therapy. **KEY WORDS** *CYP2D6*; β_1 -adrenergic receptor; genetic polymorphism; essential hypertension; metoprolol

Pharmacogenomics is a rapidly emerging field that aims to elucidate the genetic basis for inter-individual differences in drug response, using genome wide approaches to identify genetic polymorphisms that govern individual response to specific drugs^[1-4]. As described in the initial reports from the human genome project, there are over 1.4 million single nucleotide polymorphisms (SNPs) in the human genome, with over 60000 of these residing in the coding region of human genes, and the number of SNPs will grow as more humans are studied. Some of these SNPs have already been associated with significant changes in the metabolism or effects of commonly used drugs and are beginning to make their way into clinical medicine as molecular diagnostics^[5]. For some genetic polymorphisms (for example, cytochrome P450 2D6), monogenic traits have a marked effect on drug disposition (for example, pharmacokinetic changes attributable to aberrant drug metabolism), and people who inherit the enzyme deficiency must be treated with substantially different doses of

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some affected drugs^[6-8]. Likewise, polymorphisms in drug targets (for example, β_2 adrenoceptor, 5-lipoxygenase) have been shown to change the sensitivity of patients to treatment with medications that interact with these targets (for example, β agonists, zileuton), changing the pharmacodynamics of drug response^[9,10].

β -blockers are widely used in the management of hypertension^[11]. However, there is a considerable inter-individual and interethnic variability in the response to β_1 -adrenergic receptor antagonist^[12-14]. Several studies have elucidated that changes in the heart rate or blood pressure after administration of β -blockers, even highly β_1 -selective ones, vary widely among healthy or hypertension subjects, with adequate blood pressure control failing to be achieved with β -blocker mono-therapy in 30% to 60% of patients^[15,16].

With the recognition that functionally significant genetic polymorphisms of the β_1 -adrenergic receptor exist with clinically relevant allelic frequency, we hypothesized that β_1 -adrenergic receptor haplotype may account for an element of the variability in the response to metoprolol in essential hypertension patients.

Because most drug effects are determined by the interplay of several gene products that govern the pharmacokinetics and pharmacodynamics of medications, pharmacogenomics is increasingly focused on elucidating polygenic determinants of drug effects.

Metoprolol, a common used selective β_1 -blockade, is metabolized by polymorphic drug metabolizing enzymes CYP2D6^[17]. CYP2D6 activity is controlled by multiple alleles^[18]. These alleles have different effects on CYP2D6 activity. CYP2D6 enzymes which is encoded by the alleles of *CYP2D6* *1 and *CYP2D6* *2 have a normal activity. But CYP2D6 enzymes which is encoded by the alleles of *CYP2D6* *5 and *CYP2D6* *10 have a lower activity^[19]. Previous studies showed that *CYP2D6* *10 was the most common allele in Chinese^[20]. With the recognition that functionally significant genetic polymorphisms of the β_1 -adrenergic receptor and *CYP2D6* *10 exist with clinically relevant allelic frequency, we hypothesized that β_1 -adrenergic receptor and CYP2D6 genetic polymorphism may account for an element of the variability in the response to metoprolol in essential hypertension patients.

1 MATERIALS AND METHODS

1.1 Subjects The study protocol was approved by the Ethics Committee of Xiangya School of Medicine, Central South University. One hundred and twenty-five (male, 70; female, 55) unrelated essential hypertension patients aged 38—67 was recruited after giving their written informed consent. Hypertension was defined as untreated (for at least 2 weeks) sitting (> 5 minutes) Systolic blood pressure ≥ 140 mm Hg (1 mm Hg = 0.133 kPa) and/or diastolic blood pressure ≥ 90 mm Hg on two clinic visits separated by at least 3 days. Those hypertension patients' serious diseases such as kidney disease or diabetes, hypothyroidism or systemic lupus erythematosus were excluded. Patients could take medications for other indications but were excluded if any of these medications could conceivably affect blood pressure. Table 1 shows the characteristic profile of hypertension patients.

All of them were Chinese Han nationality living in Xiangtan city, Hunan province, China. All the subjects were not smoker and abstained from coffee and alcohol for a week before the study. A 5-mL blood sample for isolation of genomic deoxyribonucleic acid (DNA) was collected.

Table 1 Characteristics of essential hypertension patients

Characteristics	Value
Age(year)	51 \pm 8
Gender(male/female)	70/55
Body Mass Index (kg/m ²)	23.4 \pm 2.3
Heart Rate (beat per min)	74 \pm 6.8
Systolic Blood Pressure (mm Hg)	154 \pm 6.4
Diastolic Blood Pressure (mm Hg)	93 \pm 8.1
Mean Arterial Pressure (mm Hg)	116 \pm 7.1
Disease Duration (year)	2.3 \pm 1.7

1.2 Protocol After completion of baseline studies, patients began taking metoprolol at a dose of 12.5 mg, Bid. Thus the time for up-titration was a period of 4 weeks, the dosing regimen of metoprolol could be adjusted by the clinician. Total follow up time was 12 weeks.

1.3 Genotyping procedures for β_1 -adrenergic receptor Genomic DNA was extracted from peripheral lymphocytes with phenol-chloroform followed by ethanol precipitation. Genotyping analysis was conducted by the

polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The PCR of β_1 -adrenergic receptor gene was performed as described previously with minor modification. Because the cDNA sequence of human β_1 -adrenergic receptor gene was GC-rich, a commercial advantage GC-rich genomic PCR buffer (TaKaRa Biotech, China) was used to obtain more legible bands in electrophoresis. For the Ser49Gly locus, we used the primer pair as follows: the sense primer P1 (5'-CCGGGCTTCTGGGGTGTTC-3') and the antisense primer P2 (5'-GGCGAGGTGATGGCGAGGTAGC-3'). The final 25 μ L PCR mixture contained 5.25 μ L of PCR grade water, 12.5 μ L of 2(PCR buffer (Mg^{2+}), 4 μ L of dNTPs (2.5 μ mol/L each), 1.5 μ L of primer (10 μ mol/L each), 0.25 μ L of Taq DNA polymerase (5 U/ μ L, TaKaRa Biotech, China) and 1.5 μ L of genomic DNA sample. Temperature cycling proceeded as follows: initial denaturation for 1 min at 94 °C followed by 30 cycles of 30 s at 94 °C, 1 min at 62 °C, 1 min at 72 °C and a terminal extension for 7 min at 72 °C. The Gly389Arg polymorphic locus was amplified by the use of the sense primer P3 (5'-CATCATGGGCGTCTTCACGC-3') and the antisense primer P4 (5'-TGGGCTTCGAGTTCACCTGC-3'). The reaction system and amplification conditions were similar to those of the A145G locus except that the denaturation temperature was 60 °C. The amplified DNA fragments including the Ser49Gly or Gly389Arg polymorphic site were separately digested with EcoO109I (TaKaRa Biotech, China) or BclI (England Biolabs, Beverly, MA) at 37 °C for 8 hours. The different patterns of the digested fragments were visualized on ethidium bromide stained 2% agarose gel.

1.4 Genotyping procedures for *CYP2D6* *10 The genotyping methods for *CYP2D6* *10 variance was performed as described previously with minor modification^[21]. summarized as follow:

Primers:

Sense primer: 5'-CCA TTT GGT AGT GAG GCA GGT AT-3'

Antisense primer: 5'-CAC CAT CCA TGT TTG CTT CTG GT-3'

Reaction system:

4.75 μ L of PCR grade water

12.5 μ L of 2(PCR buffer (Mg^{2+}))

3.0 μ L of dNTPs (2.5 μ mol/L each)

2.5 μ L of primer (10 μ mol/L each)

2.0 μ L of genomic DNA sample

0.25 μ L of Taq DNA polymerase (5 U/ μ L)

Reaction conditions:

Initial denaturation for 2 min at 94 °C

32 cycles of 30 s at 94 °C, 30 s at 52 °C, 30 s at 72 °C

Terminal extension for 7 min at 72 °C.

Digestion with restriction endonucleases:

15 μ L of PCR products

2 μ L of 10× Digestion buffer

1 μ L of *Hph* I (10 U/ μ L)

2 μ L of PCR grade water

37 °C, 8 h

The different patterns of the digested fragments were visualized on ethidium bromide stained 2.5% agarose gel.

Genotype assay:

The amplified 272 bp DNA fragments contain a *Hph* I cleavage site. The presence of T188 gave rise to a *Hph* I cleavage site. Thus cleavage of the 272 bp product into fragments of 213 and 59 bp confirmed the presence of C188 allele; cleavage of the 272 bp product into fragments of 112 bp, 101 bp and 59 bp confirmed the presence of T188 allele (Fig 1).

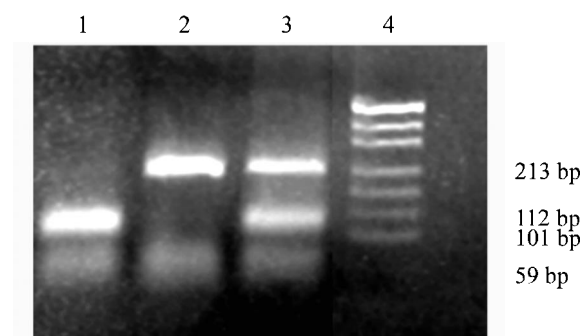


Fig 1 *Hph* I digested DNA fragments of *CYP2D6* PCR product

1: *CYP2D6* *10 *10; 2: *CYP2D6* *1 *1; 3: *CYP2D6* *1 *10; 4: DNA marker

Following the amplifications, part of PCR products were purified and sequenced to clarify the accuracy of RFLP assay (Fig 2).

1.5 Plasma metoprolol concentration measured by the use of HPLC fluorescence detection 50 μ L (50

ng/mL) of propranolol (Sigma chemical Co, USA) was added to 1 mL plasma sample as the internal standard for assaying metoprolol, both of which were extracted with dichloromethane. The aliquot of the organic layer after being shaken vigorously for 3 min and centrifuged for 10 min (3 500 r/min) was transferred to another glass tube and evaporated to dryness under a gentle stream of nitrogen at 37 °C. Residues were reconstituted by 50 μL of the HPLC mobile phase. The HPLC was performed on a 5 μm Zorbax Cs column (4.6 mm×250 mm, ID, Zorbax) at the Ex wavelength of 230 nm and the Em wavelength of 310 nm at 29.5 °C of column temperature. The mobile phase was a mixture of methanol, water, glacial acetic acid and triethylamine (70/30/0.12/0.03, v/v) at a flow rate of 1.0 mL/min. The retention times of metoprolol and the internal standard were 6.984 and 5.411 min. The intra- and inter- coefficient of variation for metoprolol assay are 3.7 % and 4.0 %, respectively.

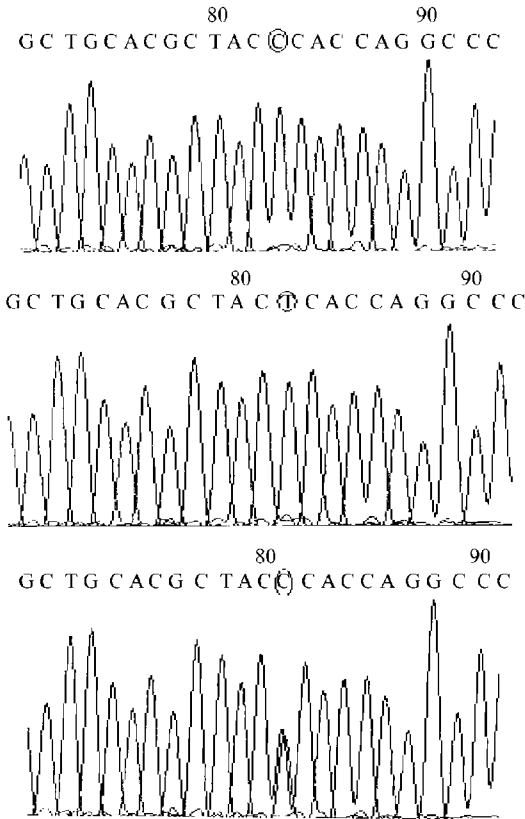


Fig 2 Sequencing results of CYP2D6 *10 variance
Upper block indicates CYP2D6 *1 *1, middle block indicates *10 *10 and lower block indicates CYP2D6 *1 *10.

1.6 Statistical analysis Data analysis was performed using SPSS (version 11.0 for Windows). Independent *t*-test was used to compare the difference in heart rate and

blood pressure between baseline and after treatment. Changes in systolic blood pressure and diastolic blood pressure were tested by unpaired *t* test or one way ANOVA, as appropriate. All values are reported as means ±SD or median and interquartile range or percentage in the figures and text. A two tail value of *P* < 0.05 was considered statistically significant.

2 RESULTS

2.1 Genotype result All the subjects could be genotyped unambiguously for Gly389Arg and Ser49Gly polymorphisms of β₁-adrenergic receptor and CYP2D6 *10 variance. When the PCR/RFLP assay of genotype was repeated for randomly selected samples, the second genotype of each sample was identical to its first one, which verified the reproducibility of the genotyping results. The allele and genotype frequencies were shown in Table 2.

Table2 Distribution characteristics of CYP2D6 *10 and β₁-adrenergic receptor genetic polymorphism in hypertension patients

Polymorphism	<i>n</i>	Frequency(%)
Ser49Gly genotypes		
49Ser/Ser	83	66.4
49Ser/Gly	41	32.8
49Gly/Gly	1	0.0
Ser49Gly alleles		
49Ser	207	82.8
49Gly	43	17.2
Gly389Arg genotypes		
389 Gly/Gly	8	6.4
389Gly/Arg	56	44.8
389Arg/Arg	61	48.8
Gly389Arg alleles		
389Gly	72	28.8
389Arg	178	71.2
CYP2D6 genotypes		
CYP2D6 *1 *1	27	21.6
CYP2D6 *1 *10	55	44.0
CYP2D6 *10 *10	43	34.4
CYP2D6 alleles		
CYP2D6 *1	109	43.6
CYP2D6 *10	141	56.4

2.2 Effects of CYP2D6 genotype on metoprolol pharmacokinetics The subjects were divided according CYP2D6 genotype and metoprolol dosage. There were significant difference in the metoprolol dosage used be-

tween various genotype groups ($P=0.003$, Table 3). After multi dosage, metoprolol trough concentraton (C_0) were associated with CYP2D6 genotype (Table 4).

Table 3 Metoprolol concentration in essential hypertension patients with different CYP2D6 genotypes

Metoprolol dosage	Metoprolol concentration			P value *
	CYP2D6 *1 *1	CYP2D6 *1 *10	CYP2D6 *10 *10	
25 mg	4.0(2.8—7.3)(n= 5)	7.6(4.0—10.4)(n= 23)	15.6(12.9—20.2)(n= 23)	0.005
50 mg	11.9(4.5—15.1)(n= 7)	16.4(6.6—19.7)(n= 20)	27.0(25.6—35.9)(n= 13)	0.017
100 mg	17.7(11.9—28.5)(n= 15)	42.5(13.3—72.9)(n= 12)	60.2(49.2—103.2)(n= 7)	0.021

General liner model-repeat measured ANOVA $P=0.003$

Data are given as median and interquartile range or percentage.
* P values between groups with same dosage in different genotype groups
P value between groups with various dosages in different genotype groups.

Table 4 Dosage needed in patients with different CYP2D6 genotypes

Metoprolol dosage	CYP2D6 *1 *1 n(%)	CYP2D6 *1 *10 n(%)	CYP2D6 *10 *10 n(%)	P value
25 mg	5(18.5)	23(41.8)	23(53.5)	0.003
50 mg	7(25.9)	20(36.4)	13(30.2)	
100 mg	15(55.6)	12(21.8)	7(16.3)	

2.3 Effects of β_1 -adrenergic receptor and CYP2D6 genotype on metoprolol pharmacodynamics After 12 weeks of metoprolol treatment, systolic blood pressure and diastolic blood pressure were significantly decreased in each group. The extent of decrease in systolic blood pres-

sure and diastolic blood pressure were associated with β_1 -adrenergic receptor Ser49Gly and Gly389Arg genotypes. Whereas we failed to find a association between blood pressure decrease and CYP2D6 *10 genotype (Table 5).

Table 5 Effects of β_1 -adrenergic receptor CYP2D6 genetic polymorphism on metoprolol antihypertension response

Genotype	n	Systolic Blood Pressure (mm Hg)				Diastolic Blood Pressure (mm Hg)			
		Baseline	After treatment	Drug effect	Drug * genotype effect	Baseline	After treatment	Drug effect	Drug * genotype effect
Ser49Ser variance				$P<0.001$	$P=0.018$			$P<0.001$	$P=0.020$
Ser49Ser	83	155±7.2	133±6.2			94±8.1	85±7.3		
Gly49 carrier	42	156±6.8	141±4.8			95±8.0	82±6.8		
Arg389Arg variance				$P<0.001$	$P=0.034$			$P<0.001$	$P=0.001$
Arg389Arg	61	159±7.1	135±6.3			95±8.8	81±6.9		
Gly389 carrier	64	154±7.4	142±6.7			93±7.2	85±7.0		
CYP2D6 *10 variance				$P<0.001$	$P=0.196$			$P<0.001$	$P=0.278$
CYP2D6 *1 *1	27	153±6.3	141±5.8			98±7.6	85±6.5		
CYP2D6 *1 *10	43	154±7.2	139±6.2			96±8.2	82±7.2		
CYP2D6 *10 *10	43	153±7.1	137±5.9			97±7.9	84±7.7		

3 DISCUSSION

Genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and other drug targets have been linked to inter-individual differences in the efficacy

and toxicity of many medications. Pharmacogenomic studies are rapidly elucidating the inherited nature of these differences in drug disposition and effects, thereby enhancing drug discovery and providing a stronger scientific basis for optimizing drug therapy on the basis of each pa-

tient's genetic constitution^[1].

β -adrenergic receptor blockers are the most widely used agents in the treatment of congestive heart failure and hypertension^[22]. There is a considerable interindividual and interethnic variability in the response to β -adrenergic receptor antagonists^[12, 13]. Such differences may arise from genetically conditioned deficiencies in drug metabolism or in receptor sensitivity. Our study was aimed to elucidate the genetic factors that led to pharmacokinetics and pharmacodynamics difference of metoprolol antihypertension therapy.

Metoprolol is mainly metabolized by the CYP2D6. Studies show that the plasma concentrations of metoprolol has a significant relationship with CYP2D6 activity^[12, 23]. Clinical studies also showed that during the treatment with metoprolol, poor metabolizers (PMs) of cytochrome P450 CYP2D6 had a 5-fold higher risk of having adverse drug reactions compared with extensive metabolizers (EMs)^[24]. Our study find that, after multi-dose of metoprolol administration, metoprolol trough concentration (C_0) was associated with *CYP2D6* *10 variance, with the concentration was increased in order in *CYP2D6* *1 / *1, *CYP2D6* *1 / *10 and *CYP2D6* *10 / *10 patients, according to a genedose effect. Our data also suggested that the heart failure patients with the *CYP2D6* *1 / *1 and those with the *CYP2D6* *1 / *10 genotypes were significantly more likely to require increases in heart failure medications during beta-blocker titration than patients with *CYP2D6* *1 / *1 genotype. Our result was in consistence with others and indicated that genetic polymorphism of CYP2D6 is a determinant for metabolize of metoprolol. Whereas, our study failed to find a significant effect of CYP2D6 genotype on blood decrease in hypertension patients after metoprolol therapy.

There are many examples for genetic variance of receptor associated with altered drug response. Among which, β_2 -adrenergic receptor ranks among the most cited examples of therapeutic consequences resulting from receptor polymorphisms. Several SNPs were shown have profound effects on β_2 -adrenergic receptor function when expressed as single mutations of the wildtype receptor in heterologous cells. children with asthma carrying the rather common R16G variant have been suggested to be less responsive clinically to β_2 -adrenergic receptor agonists,

presumably because the receptor is down-regulated by therapy *in vivo*^[25-28]. In the case of the 5-HT_{2A} and C receptors, these variants maybe associated with altered response to clozapine in the treatment of schizophrenia. This has been tested in some detail for clozapine by Arranz *et al*^[29, 30].

Our study indicated that, after 12 weeks metoprolol therapy, Gly49 carriers had stronger decrease in systolic and diastolic blood pressure than that of Ser49 homozygotes. Similarly, subjects homozygous for Arg389 had stronger decrease in blood pressure than that of Gly389 carriers. Because plasma metoprolol concentrations did not show significant effect on the extent of blood pressure decrease, we can infer from our results that the altered response reflected a difference in the sensitivity of receptors with various genotypes.

In summary, our study provided useful information for tailored drug therapy.

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β₁ 肾上腺素受体与 CYP2D6 基因多态性对美托洛尔 抗高血压治疗的药代动力学和药效学影响

摘要 背景: 美托洛尔是临床常用的抗高血压药物,它经由 CYP2D6 代谢。CYP2D6 * 10 降低 CYP2D6 活性,是中国人中最为常见的多态性。β₁ 肾上腺素受体为美托洛尔的作用靶标, Ser49Gly 与 Gly389Arg 多态性显著改变受体功能。CYP2D6 与 β₁ 肾上腺素受体遗传多态性对美托洛尔降压疗效的联合影响仍属未知。**目的:** 发现与美托洛尔药代动力学与药效动力学相关的基因多态性位点。为提高高

血压病的疗效和减少不良反应提供实验依据。**方法:** 符合 WHO/ISH 高血压诊断标准的轻、中度高血压患者 125 例,服用美托洛尔单药治疗 12 周,每四周检测血压。在临床观察疗效的同时,应用 PCR-RFLP 方法对患者进行 CYP2D6 * 10 与 β₁ 肾上腺素受体 Ser49Gly 和 Gly389Arg 基因型分析。同时抽取静脉血 5mL,高效液相色谱-荧光检测法测定患者美托洛尔谷浓度。**结果:** 美托洛尔谷浓度与 CYP2D6

*10 基因型显著相关,并呈基因剂量效应。但高血压患者血压降低程度在 *CYP2D6* *1 *1、*1 *10 与 *CYP2D6* *10 *10 组间无差异。Gly49 携带者服用美托洛尔后收缩压与舒张压的降低显著大于 Ser49Ser 纯合子;与 Gly389 携带者相比,Arg389Arg 服用美托洛尔后收缩压与舒张压的降低更为显著,表明 Gly49 与 Arg389 型受体对美托洛尔治疗有较好

的敏感性。**结论:** *CYP2D6* *10 突变显著改变美托洛尔的药代动力学,但对美托洛尔的降压效果无显著性影响。 β_1 肾上腺素受体遗传多态性与 β 受体阻滞药的降压敏感性有一定相关性。

关键词 *CYP2D6*; β_1 肾上腺素受体;遗传多态性;原发性高血压;美托洛尔