

Basic Study

β -2 Adrenergic receptor gene polymorphism and response to propranolol in cirrhosis

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Abstract

AIM: To evaluate the association of β -2 adrenergic receptor (β_2 -AR) gene polymorphism with response of variceal pressure to propranolol in cirrhosis.

METHODS: Sixty-four non-related cirrhotic patients participated in this study and accepted variceal pressure measurement before and after propranolol administration. Polymorphism of the β_2 -AR gene was determined by directly sequencing of the polymerase chain reaction products from the DNA samples that were prepared from the patients.

RESULTS: The prevalence of Gly16-Glu/Gln27 and Arg16-Gln27 homozygotes, and compound heterozygotes was 29.7%, 10.9%, and 59.4%, respectively. Patients with cirrhosis with Gly16-Glu/Gln27 homozygotes had a greater decrease of variceal pressure after propranolol administration than those with Arg16-Gln27 homozygotes or with compound heterozygotes ($22.4\% \pm 2.1\%$, $13.1\% \pm 2.7\%$ and $12.5\% \pm 3.1\%$, respectively, $P < 0.01$).

CONCLUSION: The variceal pressure response to propranolol was associated with polymorphism of β_2 -AR gene. Patients with the Gly¹⁶-Glu/Gln²⁷ homozygotes probably benefit from propranolol therapy.

Key words: Variceal bleeding; β_2 -adrenergic receptor; Propranolol; Variceal pressure; Homozygotes

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Core tip: The study explored the influence of β_2 -adrenergic receptor (β_2 -AR) polymorphism and the response of esophageal variceal pressure to chronic treatment with propranolol. The originality was that we associated the polymorphism to the measurement of variceal pressure and considered the response to propranolol administration. We found that the variceal pressure response to propranolol was associated with β_2 -AR gene polymorphisms, and that the patients with the Gly16-Glu/Gln27 homozygotes seem to benefit more from propranolol therapy.

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INTRODUCTION

Variceal bleeding is a severe complication of patients with liver cirrhosis and portal hypertension. More than 40% of cirrhosis patients have esophageal varices at the time of diagnosis. Nearly 30% of those patients with large esophageal varices will bleed within 2 years^[1]. Nonselective β -blockers are effective in preventing first variceal bleeding in patients with cirrhosis^[2-4] because these drugs can reduce portal pressure^[5,6]. Previous studies have reported that variceal bleeding can be effectively prevented by a decrease in hepatic venous pressure gradient (HVPG) < 12 mmHg after prophylactic propranolol therapy, or spontaneously^[6,7]. Additionally, previous studies have demonstrated that patients with a decrease in HVPG from baseline of $\geq 20\%$ have a low risk of first variceal bleeding and rebleeding^[8,9], even if the final HVPG is > 12 mmHg^[10-13].

Although the nonselective β -blockers decrease the portal pressure in cirrhosis patients, the response is not uniform. In a study involving 60 cirrhosis patients, 24 showed no reduction or even a slight increase in HVPG with propranolol^[14]. Some patients who took the maximum tolerated dose of propranolol still had frequent bleeding, and did not display a significant decrease in the level of HVPG. Previous studies have found that β_2 -adrenergic receptor (β_2 -AR) was polymorphic within the human population and that polymorphism of β_2 -AR gene plays a key role in modulating cardiovascular function. A more detailed study indicated that the two most common single nucleotide polymorphisms (SNPs) determine the hemodynamic response to propranolol occur at codons 46 and 79^[11]. Several studies in healthy participants

have shown that Gly16-Glu/Gln27 homozygotes express an upregulatory vasodilatory response to local infusions of receptor agonists, whereas Arg16-Gln27 homozygotes express a downregulatory vasodilatory response^[15-17]. Patients with cirrhosis with Gly16-Glu/Gln27 homozygotes have a greater decrease in heart rate, cardiac index, and hepatic blood flow after propranolol administration than those with Arg16-Gln27 homozygotes. However, the HVPG responses to propranolol are similar in both groups^[12]. Previous studies evaluated only an acute HVPG response to intravenous propranolol administration according to β_2 -AR gene SNPs, and did not take variceal pressure (VP) into account. VP is a major predictor of variceal bleeding risk; hence, it is an important marker of the response to pharmacological therapy in patients with portal hypertension^[18-21].

Therefore, the aim of our study was to evaluate the association between VP response to propranolol and β_2 -AR gene polymorphism, and the prevalence of β_2 -AR gene polymorphisms in a small subgroup of patients with esophageal varices.

MATERIALS AND METHODS

Selection of patients

Between January 2010 and December 2012, a group of 64 cirrhotic patients (43 male and 21 female) were randomly selected to participate in the study. Their ages ranged from 18 to 70 years (median 50 years). All the patients were diagnosed with cirrhosis by liver biopsy and clinical, biochemical, endoscopic and ultrasonographic criteria. Esophageal varices were detected *via* upper gastrointestinal endoscopic examination. The causes of hepatic cirrhosis were hepatitis B virus ($n = 51$), alcohol ($n = 7$), cryptogeny ($n = 5$) and primary biliary cirrhosis (PBC, $n = 1$). Patients with the following criteria were excluded from the study: severe clotting defects, hepatic encephalopathy grade III and IV; Child-Pugh score > 12 points; multifocal hepatocellular carcinoma; contraindications to β -blocker therapy; pregnancy; or refusal to participate in the study. Patients with the VP < 15.2 mmHg were also excluded, along with patients who had undergone endoscopic interventions, including endoscopic variceal ligation and endoscopic injection sclerotherapy. The study was approved by the Ethics Committee of Anhui Medical University, and all patients gave written informed consent. A 2-mL venous blood sample was obtained from each patient and stored at -80°C for further genotypic analysis.

Study design and VP measurement

Measurement of VP was performed after an overnight fast during upper gastrointestinal endoscopy. Somatostatin infusion was stopped 2 h before starting VP measurement. VP was assessed with a previously described noninvasive technique using an esophageal

variceal manometer (EVM; Esophageal Varix Manometer; Treier Endoscopie AG, Beromünster, Switzerland) and recorded by a workstation that was developed by our team^[22]. Before VP measurement, all patients were sedated with 5 mg diazepam and 20 mg n-butylscopolamine intravenously. In previous studies, VP measured by this method had a good correlation with that measured by needle puncture^[23,24]. The largest varix of the distal esophagus was chosen for VP measurement. VP in each patient was measured five times. VP was recorded as the mean of five determinations that were taken during the procedure.

After VP measurement, the scales in the balloon markers (5-mm intervals) were used to assess variceal size. The maximal variceal size and esophageal variceal findings were recorded as proposed by the Japanese Society for portal hypertension^[25]. After baseline measurement, propranolol was given orally at an initial dose of 20 mg three times daily and was increased by 20 mg every day over a period of 7 d until the resting heart rate was reduced by 25%, or was < 55 beats/min^[4]. VP was assessed again at 7 d of propranolol administration.

Two β_2 -AR gene functional SNPs were selected for genotyping in this study: Arg16Gly and Gln27Glu.

Genotyping

Genomic DNA was extracted from the prefabricated blood samples for genotype analysis. Two β_2 -AR SNPs, Arg16Gly and Gln27Glu, were analyzed by allele-specific polymerase chain reaction (AS-PCR). The primers were designed as described previously^[12]. For the Arg16Gly site, the upstream primer of Arg16 was 5'-CTTCTTGCTGGCACCCAATA-3', while that of Gly16 was 5'-CTTCTTGCTGGCACCCAATG-3', and the downstream primer was 5'-CCAATTTAGG-AGGATGTAACTTC-3'. For analysis of the Gln²⁷Glu site, the following primers were designed, the upstream primer of Gln²⁷ was 5'-GGACCACGAC-GTCACGCAGC-3', and that of Glu27 was 5'-GGACCAC-GACGTCACGCAGG-3', and the downstream primer of both was 5'-ACAATCCACACCATCAAGAAT-3'. The reaction was performed in a 50- μ L mixture as follows: DNA template 2 μ L, each primer 1 μ L, dNTP 1 μ L, Pfu DNA polymerase 1 μ L, 10 \times Buffer 5 μ L (containing Mg²⁺ 20 mmol/L), deionized distilled water 39 μ L. The PCR was performed with an initial 94 °C for 5 min (pre-degeneration), followed by 35 cycles (94 °C for 2 min, degeneration; 55 °C for 1 min, annealing for Arg¹⁶Gly, and 52 °C for 1 min for Gln²⁷Glu; 72 °C for 1 min for polymerization), and a final step at 72 °C for 10 min to finish the reaction. The PCR products were separated at 100 V for 50 min on a 1% agarose gel and were visualized with ethidium bromide staining.

Calculation of sample size

Sample size was calculated to detect differences

between groups with different polymorphisms in VP decrease from baseline of $\geq 10\%$ after oral propranolol, with a common variance of 40. With an expected prevalence of 15% in the lower frequent homozygotes (Arg¹⁶-Gln²⁷) among the general population^[26,27], it was estimated that 47 patients would be required in the study, to achieve 80% power at the 5% level of significance.

Statistical analysis

Quantitative data were expressed as mean \pm SD and were compared using Student's *t* test. One-way ANOVA followed by pre-planned analysis was used to compare the differences between the groups with different polymorphisms. Comparisons of categorical variables between different groups were performed using Fisher's exact test. Statistical analysis was done using SPSS version 12.0 software. Statistical significance was defined as $P < 0.05$.

RESULTS

Genotype analysis

We used the AS-PCR to test β_2 -AR SNPs in 64 individuals. The frequencies for three homozygotes were Gly¹⁶/Glu²⁷ = 28.1%, Gly¹⁶/Gln²⁷ = 1.6%, Arg¹⁶/Gln²⁷ = 10.9%, and compound heterozygotes = 59.4%. No significant differences were seen in baseline characteristics between the groups of different polymorphisms (Table 1).

Baseline VP and response to propranolol

All patients had severe portal hypertension as shown by VP > 15.2 mmHg and the presence of esophageal varices. No significant differences were seen in the baseline VP among homozygous haplotypes (Table 1).

As expected, propranolol administration (80-160 mg/d, median: 120 mg/d) caused a significant decrease in heart rate in each group. The median daily dose of propranolol was 105 \pm 34 mg in the Arg16-Gln²⁷ homozygotes, 113 \pm 38 mg in the Gly16-Glu/Gln²⁷ homozygotes, and 108 \pm 35 mg in the compound heterozygotes. There were no significant differences among haplotypes ($P > 0.05$). We also found that Gly16-Glu/Gln²⁷ homozygotes had a greater reduction in heart rate than Arg16-Gln²⁷ homozygotes (-20.2% \pm 1.4% vs -14.8% \pm 2.2% respectively, $P = 0.03$) (Table 2). Compound heterozygotes were found to have intermediate response compared to those homozygotes after oral propranolol treatment (-16.9% \pm 2.9%).

As shown in Table 2, the reduction of VP was significant after propranolol administration in each group. The percentage VP reduction in the Gly¹⁶-Glu/Gln²⁷ homozygotes was significantly greater than that in the Arg¹⁶-Gln²⁷ homozygotes or compound heterozygotes (22.4% \pm 2.1%, 13.1% \pm 2.7% and

Table 1 Demographic profile of the study population

	Arg ¹⁶ -Gln ²⁷ (<i>n</i> = 7)	Compound heterozygotes (<i>n</i> = 38)	Gly ¹⁶ -Glu/Gln ²⁷ (<i>n</i> = 19)	<i>P</i> value
Sex (M/F)	5/2	27/11	11/8	0.630
Age (yr), mean ± SD	51.60 ± 10.91	49.02 ± 22.52	51.95 ± 8.76	0.733
Etiology				
Hepatitis B	5	32	14	0.425
Alcohol	1	4	2	
Cryptogenic	1	1	3	
Primary biliary cirrhosis	0	1	0	
Alcohol intake, Y/N	0/7	6/32	3/16	0.756
History of bleeding, Y/N	2/5	8/30	5/14	0.858
Ascites, Y/N	0/7	11/27	5/14	0.332
Albumin, g/L	32.88 ± 5.85	32.36 ± 5.63	33.13 ± 4.72	0.668
Total bilirubin (μmol/L)	46.99 ± 35.92	40.76 ± 23.91	52.61 ± 69.65	0.072
Prothrombin time (s)	16.18 ± 2.23	15.84 ± 2.30	15.22 ± 2.56	0.713
Serum sodium (mmol/L)	138.50 ± 5.43	138.30 ± 4.74	139.12 ± 4.8	0.768
Child-Pugh score	6.86 ± 1.21	6.61 ± 1.52	6.74 ± 1.91	0.168
VP (mmHg)	21.35 ± 3.02	22.08 ± 3.26	21.69 ± 2.78	0.367

Table 2 Heart rate and VP changes after propranolol according to β₂-AR gene polymorphisms

Variables	Gly ¹⁶ -Glu/Gln ²⁷ (<i>n</i> = 19)		Compound heterozygotes (<i>n</i> = 38)		Arg ¹⁶ -Gln ²⁷ (<i>n</i> = 7)	
	Baseline	7 d	Baseline	7 d	Baseline	7 d
HR (beats/min)	76.3 ± 2.7	60.5 ± 1.8 ^b	75.6 ± 4.9	62.5 ± 3.6 ^b	74.1 ± 4.7	62.9 ± 3.0 ^a
VP(mmHg)	21.35 ± 3.02	16.52 ± 1.87 ^b	22.08 ± 3.26	19.43 ± 3.12 ^a	21.69 ± 2.78	18.79 ± 3.15 ^b

^a*P* < 0.05, ^b*P* < 0.01 vs baseline. HR: Heart rate.

12.5% ± 3.1%, respectively, *P* < 0.01).

DISCUSSION

Propranolol is a nonselective β-AR blocker and has been used to prevent variceal bleeding for many years. Propranolol prevents variceal bleeding and reduces HVPg *via* blocking β₁-AR to decrease cardiac output, heart rate and cardiac constriction, and *via* blocking β₂-AR to contract splanchnic veins and reduce splanchnic and portal blood flow^[13,14,28]. However, the effect of propranolol varies in different patients and the drug fails to reduce of HVPg level in some patients who have a high risk of bleeding and mortality^[29]. The discrepancy in the effect of propranolol in preventing variceal bleeding has attracted much research interest worldwide^[30-32].

Recently, in an attempt to explore the role of β-AR in the regulation of vascular tension and hemodynamic response to β-AR, it was found that β₂-AR gene polymorphisms played a key role in modulating cardiovascular function in humans^[31,32]. In particular, two common mutations of β₂-AR gene, +46 site G to A mutation and +79 site C to G mutation resulted in a change of amino acids of β₂-AR from Arg¹⁶ to Gly¹⁶ and Gln²⁷ to Glu²⁷, which played a little or no role in affecting the state of illness. However, it might affect the response of propranolol administration individually^[33,34].

Furthermore, it was found that homozygotes

Gly¹⁶Gly or Glu²⁷Glu genotype individual exhibit an enhanced vasodilatory response to isoproterenol infused through bronchial artery or arm vein locally^[15-17]. A similar result was obtained for therapy of asthma with β₂-adrenergic agents^[35,36]. However, a study evaluating the role of β₂-AR gene SNPs in portal hypertension is still lacking. There are individual discrepancies in the preventive effect of propranolol on variceal bleeding that might be associated with β₂-AR SNPs. Patients with Gly¹⁶Gly or Glu²⁷Glu homozygote genotype might benefit more from propranolol administration than those with Arg¹⁶ or Gln²⁷ alleles^[12]. Nevertheless, that study only revealed an acute HVPg response to intravenous administration of propranolol, and the VP response to oral propranolol is still unknown. Previous studies have demonstrated that VP is a major predictor of variceal bleeding risk and the response to pharmacological therapy in patients with portal hypertension^[18-21]. For example, a VP level ≥ 15.2 mmHg represents a high risk of variceal bleeding in patients with cirrhosis^[19]. Therefore, studies on the VP response to propranolol treatment have clinical significance.

The present study assessed the prevalence of β₂-AR gene polymorphism in a small subgroup of patients with cirrhosis. The prevalence of Gly¹⁶-Glu/Gln²⁷ and Arg¹⁶-Gln²⁷ homozygotes, and compound heterozygotes was 29.7%, 10.9%, and 59.4%, respectively. These data are similar to those in western studies and the US^[12,26,27,37]. No significant

differences in the basal heart rate and VP regarding the different β_2 -AR haplotypes were found before propranolol administration. An important result from our study was that patients with cirrhosis and portal hypertension showed different responses to propranolol, as calculated by the reduction in VP. After administration of propranolol, patients with the Gly¹⁶-Glu/Gln²⁷ homozygotes showed a greater reduction in VP, whereas patients with Arg¹⁶-Gln²⁷ homozygotes exhibited a lesser reduction. The individuals who were compound heterozygotes had an intermediate response between Gly¹⁶-Glu/Gln²⁷ and Arg¹⁶-Gln²⁷ homozygotes.

The limitation of our study was that prevalence of β_2 -AR gene polymorphisms was investigated in a small subgroup of patients with cirrhosis, so, the assessment was not accurate. A prospective follow-up study of cirrhosis patients is underway to investigate the prevalence of β_2 -AR gene polymorphisms and analyze the impact of the polymorphisms on the hemodynamic effect of propranolol in esophageal varices.

In summary, we discovered that the individual differentiation of the effect of propranolol is associated with β_2 -AR 46 SNP. The replacement of amino acid 16 in the receptor from Arg to Gly results in an enhanced response to propranolol. Patients with an allele gene Gly benefit more from propranolol therapy than those with an Arg in long-term treatment.

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COMMENTS

Background

Although β -blockers decrease the portal pressure in many cirrhosis patients, the response is not uniform. It was found that β_2 -adrenergic receptor (β_2 -AR) gene is polymorphic within the human population and that the polymorphisms play a key role in modulating cardiovascular function. A more detailed study indicated that the two most common single nucleotide polymorphisms (SNPs) determined the hemodynamic response to propranolol occurred at codons 46 and 79. It was clear that β_2 -AR gene polymorphisms influenced the response of variceal pressure (VP) to propranolol in patients with cirrhosis.

Research frontiers

The authors explored whether β_2 -AR gene polymorphism influenced the response of VP to propranolol in patients with cirrhosis.

Innovations and breakthroughs

The authors found that the VP response to propranolol was associated with polymorphism of β_2 -AR gene. Patients with the Gly¹⁶-Glu/Gln²⁷ homozygotes probably benefited from propranolol therapy.

Applications

The results suggest that the patients with an allele gene Gly benefit more from propranolol therapy than those with an Arg in long-term treatment.

Terminology

The individual differentiation of the effect of propranolol is associated with β_2 -AR 46 SNP. The replacement of amino acid 16 in the receptor from Arg to Gly results in an enhanced response to propranolol. Patients with the Gly¹⁶-Glu/Gln²⁷ homozygotes probably benefit from propranolol therapy.

Peer-review

The paper evaluates the association between the effects of propranolol, variceal pressure and β_2 -AR gene polymorphism in a group of 64 non-related Chinese cirrhotic patients. The authors found that the variceal pressure response to propranolol was associated with β_2 -AR gene polymorphisms, and that the patients with the Gly¹⁶-Glu/Gln²⁷ haplotypes seem to benefit more from propranolol therapy. This is an interesting paper, with original data.

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