

Dose-dependent effect of propranolol on the hemodynamic response in cirrhotic patients with gastroesophageal varices

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Objective Propranolol is always titrated to the maximum tolerated dose to prevent gastroesophageal variceal bleeding. However, some patients do not achieve a hemodynamic response and experience more intolerance and discontinuation. This study evaluated the dose-dependent effect of propranolol on hemodynamic response and tolerance in cirrhotic patients.

Patients and methods This retrospective study included 95 consecutive patients recruited from our prospective database. After hepatic venous pressure gradient measurement, patients received propranolol 10 mg, twice daily increased 10 mg daily until to 80 or 120 mg/day. Secondary hepatic venous pressure gradient was also measured. For nonresponders at 80 mg/day, propranolol was titrated to 120 mg/day.

Results For 58 patients, propranolol was titrated to 80 mg/day, whereas for 37 patients, it was titrated to 120 mg/day. Hemodynamic response was similar in both groups (50 vs. 54.1%, $P=0.700$). Eighteen of the 29 nonresponders at propranolol 80 mg/day received a dose of 120 mg/day. Two patients achieved a hemodynamic response, but two could not tolerate the dose. Nine (15.5%) patients achieved the target dose of propranolol at 80 mg/day, whereas 16 (43.2%) patients at 120 mg/day achieved this ($P=0.003$). The difference in patients achieving the target dose between responders and nonresponders was not significant (14 vs. 14, $P=0.642$). Reduction or discontinuation was required by two (6.9%) patients using 80 mg/day propranolol and six (30%) patients using 120 mg/day propranolol ($P=0.032$).

Conclusion There is no dose-dependent effect of 80–120 mg/day of propranolol on the hemodynamic response in cirrhotic patients with gastroesophageal varices. This indicates that low-dose propranolol below the target dose might lead to a considerable hemodynamic response and is much safer and well tolerated. *Eur J Gastroenterol Hepatol* 31:368–374
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Introduction

Portal hypertension that resulted from liver cirrhosis often leads to gastroesophageal variceal bleeding, ascites, and hepatic encephalopathy. This is a common cause of morbidity and mortality worldwide. For years, nonselective β -blockers (NSBBs) have been the drug of choice for primary and secondary prophylaxis of variceal bleeding in cirrhotic patients [1]. The efficacy mainly depends on the decrease in portal vein pressure, which varies widely from patient to patient [2]. According to a number of previous studies and

practical guidelines, hemodynamic response to NSBBs has been used to evaluate the changes in portal vein pressure, which is defined as a hepatic venous pressure gradient (HVPG) reduction of at least 20% or to less than 12 mmHg [2–4]. However, many patients do not achieve the hemodynamic response to propranolol [5,6].

Propranolol is one of the most widely used NSBBs. In most published studies, the dose of propranolol was titrated to reduce the heart rate by 25% from baseline as HVPG measurement was not widely available. However, it has been proved that the reduction in heart rate does not correlate with reduction in HVPG [7,8]; therefore, the target dose of propranolol is always adjusted to the maximal tolerated dose [9]. This usually means that the dose is increased stepwise to 320 mg/day until the heart rate has decreased by 25% or below 55 bpm or the systolic blood pressure is below 90 mm Hg [7]. A newly updated guideline also showed that the therapeutic goals are a heart rate of 55–60 bpm and a systolic blood pressure not below 90 mmHg [10].

To achieve the target dose, patients often received a rather high dose of propranolol. The median dose was as high as 152.6 mg/day (40–320 mg/day) in a Korean report [11] and 160 mg/day (80–320 mg/day) in an Indian research [8]. However, the higher the dose, the more the side effects they might experience, which would lead to discontinuation or reduction of dose. The main

European Journal of Gastroenterology & Hepatology 2019, 31:368–374

Keywords: dose, hemodynamic response, liver cirrhosis, propranolol

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Received 4 August 2018 **Accepted** 18 September 2018

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disadvantage of propranolol is that 15% of patients have contraindications to therapy and another 15% require dose reduction or discontinuation because of common side effects such as fatigue, weakness, dysphagia, hypotension, shortness of breath, and sexual dysfunction [12]. Worse, the discontinuation of propranolol is up to 27–29% because of the maximal tolerated dose [13,14]. On the basis of these data, it would be relevant for us to evaluate the hemodynamic response of the different doses of propranolol below the maximal tolerated dose because the use of lower-dose drug can reduce dose-dependent side effects. To the best of our knowledge, few studies have addressed this issue. A small-sample study found that 15 patients using propranolol at 40 mg/day achieved a reduction of HVPG from 17.8 ± 1.1 to 15.1 ± 1.2 mmHg, with a response rate as high as 47% [15]. However, it is not enough to solve the problem.

The aim of this study was to evaluate the influence of different doses of propranolol on the hemodynamic response in cirrhotic patients with gastroesophageal varices to identify suitable doses with better safety and tolerance.

Patients and methods

Patients

This retrospective study was carried out in the Department of Gastroenterology in the Affiliated Drum Tower Clinical Medical School of Nanjing Medical University. Patients were 18–80 years of age with a clear diagnosis of cirrhosis on the basis of definite radiographic findings or liver biopsy, gastroesophageal varices verified by a recent upper endoscopy procedure, and a Child–Turcotte–Pugh classification of A to B. Written informed consent was obtained. Finally, 108 consecutive patients recorded in our prospective database between January 2015 and January 2018 were screened. Patients with portal vein thrombosis or cavernous transformation of the portal vein, contraindications to NSBBs, failed HVPG procedure, baseline HVPG of less than 12 mmHg, severe infections, malignant tumors, and significant cardiopulmonary or renal comorbidities were excluded. Therefore, eight patients were excluded because of an HVPG value below 12 mmHg. HVPG measurement failed in five patients because of severe hepatic vein–vein shunt in three patients and failure of the hepatic vein catheterization in two patients. In the analysis, in 58 patients, propranolol was titrated to 80 mg/day and in 37 patients, it was titrated to 120 mg/day (Fig. 1). The entire study was carried out following the principles of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Nanjing Medical University Drum Tower Clinical Medical School.

Administration of propranolol and clinical data collection

After the initial HVPG measurement, all the patients received oral propranolol (Jiangsu Yunyang Pharmaceutical Group Co. Ltd., Danyang, China) at 10 mg twice a day. The dose was increased by 10 mg stepwise daily until up to 40 or 60 mg twice a day or until the target dose was achieved, which was defined as a decrease in heart rate by 25% or less than 55 bpm or a systolic arterial pressure of less than 90 mmHg [7,16]. The secondary HVPG was then measured

7 days after the initial one. According to previous studies and practice guidelines, hemodynamic response was defined as an HVPG reduction of at least 20% or to less than 12 mmHg [2–4,11]. All the others were considered ‘non-responders’. The dose of propranolol was titrated to 120 mg/day for those nonresponders at a dose of 80 mg/day depending on the patients’ choice. A third HVPG was obtained after that. Patients’ demographics, liver disease characteristics, and clinical presentation were all collected. Basal arterial pressure and heart rate were recorded every morning during the study. For hemodynamic responders, propranolol was continued at the current dose, whereas, for nonresponders, propranolol was stopped. All potential and severe adverse drug events were reported. Once such an event was identified, the drug was stopped. If the occurrence of intolerance persisted (systolic blood pressure of <90 mmHg or heart rate of <55 bpm), the dose of propranolol was reduced stepwise and eventually stopped. Patients’ follow-up was performed by telephone calls and outpatient clinic visits each week for 1 month to investigate the tolerance and safety of the medication.

Hemodynamic measurements

HVPG procedures were performed using the techniques described previously [7,16]. The RUPS-100 (COOK, Bloomington, Indiana, USA) was placed in the inferior vena cava through the right internal jugular vein using the Seldinger technique. A 7-F balloon-tipped catheter (Edwards Lifesciences, Irvine, California, USA) was guided into the middle or the right hepatic vein. Both wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) were obtained and repeated three times, and the mean value was calculated. A small amount of radiologic contrast medium was injected manually to check the adequacy of occlusion. The difference between the mean WHVP and the mean FHVP was defined as HVPG. Heart rate and arterial pressures were monitored throughout the examination. The procedures for HVPG measurement were performed by chief physicians with over three-year experience.

Statistical analysis

Continuous data were expressed as the mean \pm SD. A *t*-test was used for continuous data, whereas the χ^2 -test was used for counting material. All analyses were carried out mainly using both intention-to-treat (ITT) and per-protocol (PP) principles. Values of *P* less than 0.05 were considered statistically significant. Univariate and multivariate logistic regression models were used to identify the predicting factors of HVPG response. All statistical analyses were carried out using SPSS, version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Patients’ baseline characteristics

ITT analysis was carried out on 58 patients from the propranolol 80 mg/day group and 37 patients from the propranolol 120 mg/day group. Six patients in the propranolol 120 mg/day group did not receive the full dose of 120 mg/day because of intolerance; therefore, only the

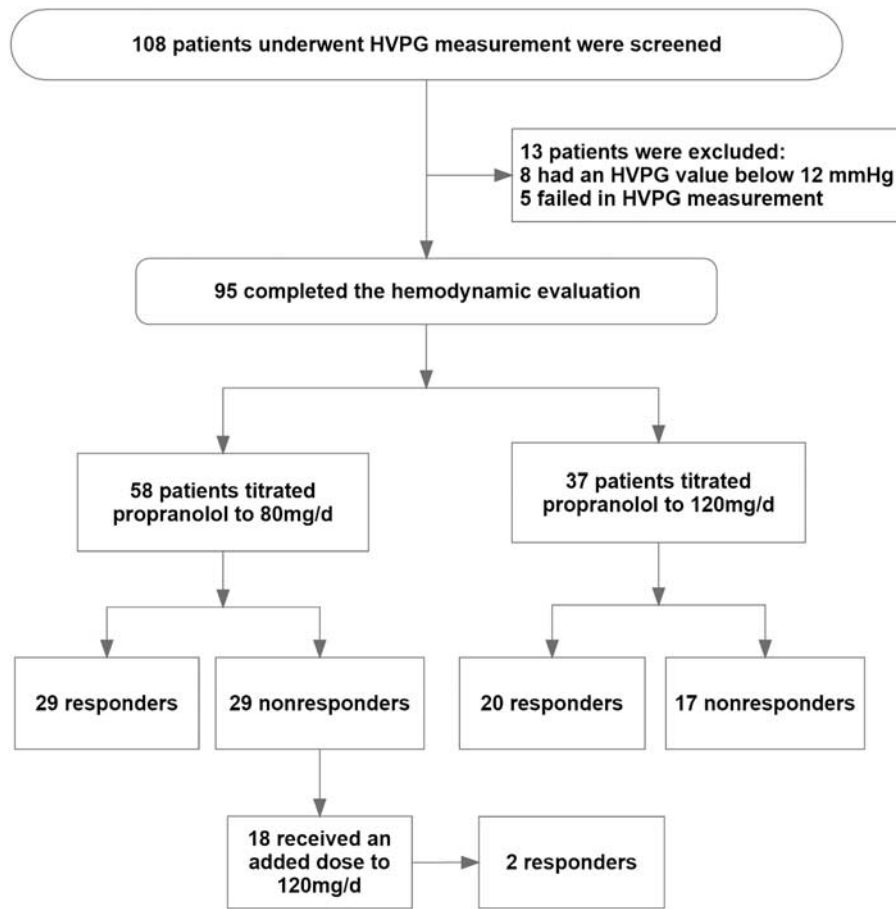


Fig. 1. Patient flow chart. HVPG, hepatic vein pressure gradient.

Table 1. Patient demographics, liver disease characteristics, and clinical presentation

Variables	Propranolol 80 mg/day (n=58)	Propranolol 120 mg/day (n=37)	P value
Age (mean±SD) (years)	51.8±13.1	55.5±8.5	0.099
Sex (male/female)	39/19	20/17	0.196
Etiology of liver cirrhosis (viral/others)	32/26	20/17	0.915
Primary/secondary prophylaxis	16/42	23/14	0.002
CTP score (mean±SD)	6.3±1.1	6.5±1.2	0.377
CTP classification (A/B/C)	30/28/0	19/18/0	0.972
Ascites (mild)	17	11	0.965
Basal heart rate (mean±SD) (bpm)	70.3±6.9	68.4±7.5	0.213
Basal SBP (mean±SD) (mmHg)	119.7±13.3	114.9±14.3	0.097

CTP, Child–Turcotte–Pugh; SBP, systolic blood pressure.

remaining 31 patients were compared with the 58 patients in the propranolol 80 mg/day group using PP analysis. Patients' characteristics are shown in Table 1. Sixteen patients received propranolol for primary prophylaxis and 42 patients for secondary prophylaxis in the propranolol 80 mg/day group. Twenty-three patients received propranolol for primary prophylaxis and 14 patients received propranolol for secondary prophylaxis in the propranolol 120 mg/day group. The differences between groups were significant. For patients receiving the secondary

prophylaxis, drug therapy had only been administered during the bleeding period. They had not received propranolol or endoscopic therapy ever. Initial endoscopic treatment was administered just after the present hemodynamic study, which included endoscopic variceal ligation or endoscopic injection sclerotherapy for esophageal varices and glue injection for gastric varices. Sequential endoscopic therapy was administered every 4 weeks until eradication of the varices. There were no significant differences in age, sex, etiology of liver cirrhosis, Child–Turcotte–Pugh score, and basal heart rate between the patients using propranolol 80 and 120 mg/day in the ITT analysis. The PP analysis also showed the same result. The mean baseline HVPG in the entire cohort was 17.6 ± 3.9 mmHg, ranging from 12 to 33.

Hemodynamic response

The hemodynamic changes are shown in Table 2. Twenty-nine (50%) patients were considered to be hemodynamic responders in the propranolol 80 mg/day group and 20 (54.1%) patients were considered to be responders in the propranolol 120 mg/day group. The difference between the groups was not statistically significant in the ITT analysis ($P = 0.700$). Four patients achieved a reduction of less than 20% to an HVPG value of less than 12 mmHg, whereas the remaining 25 patients had a reduced HVPG of at least 20% (15 of them also showed a decrease up to <12 mmHg) in the propranolol 80 mg/day group. Two patients achieved a

Table 2. Hemodynamic response to propranolol

Variables	Propranolol 80 mg/day (n=58) (mean±SD)	Propranolol 120 mg/day (n=37) (mean±SD)	P value
HVPG (mmHg)			
Baseline	17.0±2.9	18.7±4.9	0.052
Secondary	14.0±3.5	15.0±4.8	0.222
Decrease value	3.0±2.7	3.7±4.0	0.336
Decrease rate (%)	17.4±14.3	18.6±18.6	0.738
Responder [n (%)]	29 (50)	20 (54.1)	0.700
WHVP (mmHg)			
Baseline	24.9±4.6	25.9±5.6	0.340
Secondary	23.2±5.1	23.2±5.9	0.998
FHVP (mmHg)			
Baseline	7.9±3.5	7.1±2.8	0.251
Secondary	9.2±4.0	8.3±3.9	0.279
MAP (mmHg)			
Baseline	84.1±9.6	81.0±11.2	0.147
Secondary	75.6±8.8	78.0±9.7	0.228
SBP (mmHg)			
Baseline	119.7±13.3	114.9±14.3	0.097
Secondary	109.4±11.5	111.6±13.4	0.338

FHVP, free hepatic venous pressure; HVPG, hepatic vein pressure gradient; MAP, mean arterial pressure; SBP, systolic blood pressure; WHVP, wedged hepatic venous pressure.

reduction of less than 20% to an HVPG value of less than 12 mmHg, whereas the remaining 18 patients had a reduced HVPG of at least 20% (eight of them also achieved a decrease of up to <12 mmHg) in the propranolol 120 mg/day group. There were no significant differences in the baseline and secondary HVPG, WHVP, FHVP, mean arterial pressure, and systolic blood pressure between the two groups in the ITT analysis. In addition to this, the reduction in the mean HVPG was significant in both the propranolol 80 mg/day (3.0 ± 2.7 mmHg, $P < 0.001$) and the 120 mg/day (3.7 ± 7.0 mmHg, $P < 0.001$) groups; however, there was no statistically significant difference between the two groups ($P = 0.336$) (Fig. 2). Six patients could not tolerate propranolol at 120 mg/day, and the PP analysis showed similar results for the hemodynamic changes between the two groups. In the propranolol 80 mg/day group, 18 patients out of 29 nonresponders at propranolol 80 mg/day received an added dose to 120 mg/day. Two (11.1%) patients showed a hemodynamic response; however, two other patients could not tolerate the dose.

Heart rate changes to propranolol

The changes in the heart rate in both groups are shown in Table 3. Five (8.6%) patients were considered to be heart rate responders (heart rate had decreased by 25%) in the propranolol 80 mg/day group and five (13.5%) patients were heart rate responders in the propranolol 120 mg/day group. Nine (15.5%) patients achieved the target heart rate in the propranolol 80 mg/day group, whereas 16 (43.2%) patients in the propranolol 120 mg/day group achieved the target heart rate. The differences in the patients achieving the target heart rate and secondary heart rate between the two groups were statistically significant, whereas there were no significant differences in baseline heart rate, heart rate decrease value, and decrease rate. In the PP analysis, the heart rate changes were correlated with the above results. In the propranolol 80 mg/day group, 18 out of 29 nonresponders received a titrated dose of 120 mg/day, four of whom (22.2%) achieved the

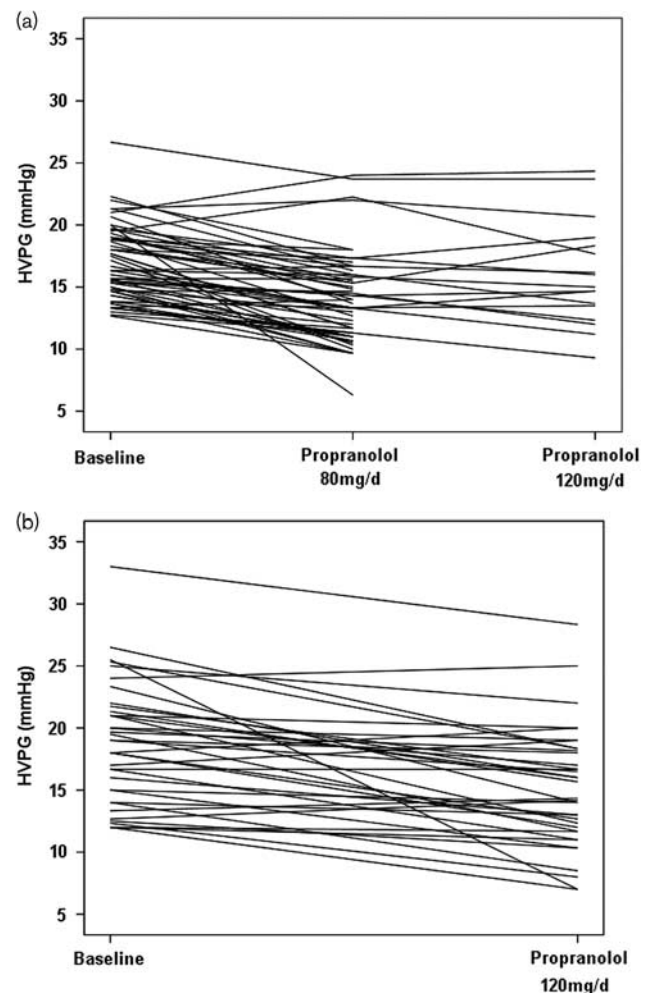


Fig. 2. Changes in the hepatic vein pressure gradient (HVPG) in individual patients receiving different doses of propranolol by an intention-to-treat analysis. (a) In the propranolol 80 mg/day group, 58 patients underwent secondary HVPG measurement for 80 mg/day and 18 nonresponders underwent a third measurement for 120 mg/day; (b) In the propranolol 120 mg/day group, 37 patients underwent secondary HVPG measurement for 120 mg/day.

target dose. In the entire cohort, 51 (53.7%) patients were hemodynamic responders, whereas 29 (30.5%) patients achieved the target dose. The number of patients who achieved the target dose among the responders and non-responders were 15 and 14, respectively. The difference was not significant ($P = 0.800$), indicating that the target dose was not correlated with the hemodynamic response.

Safety and tolerance of propranolol

In the propranolol 120 mg/day group, six patients had a target dose below 120 mg/day (three patients for 80 mg/day and three patients for 100 mg/day). Among 20 HVPG responders who needed to continue propranolol, four (20%) patients discontinued propranolol within 1 month because of side effects including hypotension and weakness, whereas in two (10%) patients, the dose was reduced to 60 and 100 mg/day, respectively, because of significantly low heart rates. In the propranolol 80 mg/day group, the dose was well tolerated by all patients during the examination. Among 29 HVPG responders for 80 mg/

Table 3. Changes in heart rate to propranolol

Variables	Propranolol 80 mg/day (n = 58) (mean ± SD)	Propranolol 120 mg/day (n = 37) (mean ± SD)	P value
Baseline heart rate (bpm)	70.3 ± 6.9	68.4 ± 7.5	0.213
Secondary heart rate (bpm)	64.0 ± 7.6	60.2 ± 7.4	0.020
Decrease value (bpm)	6.3 ± 8.3	8.2 ± 7.1	0.264
Decrease rate (%)	8.5 ± 11.3	11.6 ± 9.8	0.186
Heart rate response [n (%)]	5 (8.6)	5 (13.5)	0.449
Patients with target dose [n (%)]	9 (15.5)	16 (43.2)	0.003

Table 4. Results of univariate logistic regression analysis

Parameters	OR (95% CI)	P value
Sex (male/female)	1.587 (0.689–3.655)	0.278
Age	1.005 (0.970–1.040)	0.789
Primary/secondary prophylaxis	1.215 (0.536–2.754)	0.642
Etiology of liver cirrhosis (virus/others)	0.818 (0.364–1.838)	0.627
CTP score	1.147 (0.811–1.621)	0.438
Baseline HVPG	0.950 (0.855–1.056)	0.343
MAP reduction	1.026 (0.985–1.069)	0.222
SBP reduction	1.007 (0.979–1.037)	0.628
Dose of propranolol (80 vs. 120 mg/day)	0.850 (0.372–1.942)	0.700
Target dose	1.273 (0.508–3.188)	0.607
Heart rate reduction	1.443 (0.034–60.703)	0.848

CI, confidence interval; CTP, Child–Turcotte–Pugh; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; OR, odds ratio; SBP, systolic blood pressure.

day, the dose was reduced to 60 mg/day in only two (6.9%) patients because of a significantly low heart rate, and no patients needed to discontinue within 1 month ($P=0.032$ compared with the propranolol 120 mg/day group). Only two (11.1%) patients could not tolerate the added dose among the 18 nonresponders for propranolol 80 mg/day.

Predicting factors of hemodynamic response

Several parameters were entered into the univariate logistic regression model; however, no predicting factors were identified in line with the hemodynamic response (Table 4). The result confirmed that the HVPG response was not related to the target dose of propranolol ($P=0.607$), and there was no significant difference between propranolol 80 and 120 mg/day ($P=0.700$).

Discussion

In this study, we addressed the impact of different propranolol doses on the hemodynamic response in patients with liver cirrhosis and gastroesophageal varices. Although the HVPG response was adjusted to a decrease of at least 10% from baseline or to 12 mmHg after chronic treatment with NSBBs in primary prophylaxis in the recently published BAVENO VI consensus [1], the ‘20%’ response criteria were still used in this study to make the results more comparable to previous studies. We found no significant difference in the HVPG response rate between the patients

using propranolol 80 and 120 mg/day, which was 50 and 54.1%, respectively. Furthermore, only two patients achieved a hemodynamic response among the 18 nonresponders at the dose of propranolol 80 mg/day, with an added dose up to 120 mg/day; however, another two patients could not tolerate the dose. In contrast, patients in the propranolol 120 mg/day group achieved a significantly high target dose rate (43.2%) compared with those using propranolol 80 mg/day (15.5%), but the target dose was not correlated with the HVPG response.

In most published studies, propranolol was titrated to a target dose; however, only some of these studies reported the actual doses used, which varied widely from study to study, just like the hemodynamic response. Two recent observational studies reported the relationship between doses of propranolol and their outcomes. Bang and colleagues showed that doses of propranolol over 160 mg/day were associated with a higher mortality risk compared with nonuse of propranolol in patients with decompensated cirrhosis. Doses below 160 mg/day showed improved survival [17]. Madsen *et al.* also found that doses of propranolol below 160 mg/day were associated with improved survival in patients with spontaneous bacterial peritonitis [18]. If propranolol was titrated to the target dose according to the guidelines, the dose could be as low as 54 ± 14 mg/day [7] or as high as 152.6–160 mg/day (range: 40–320 mg/day) [8,11]. Few studies had investigated the effect of low-dose propranolol below the target dose on the hemodynamic response. Mookerjee *et al.* [19] reported a very low median dose of propranolol at 40 mg/day (range: 20–80 mg); however, the hemodynamic response and heart rate goal were unknown. Another report found that 15 patients using propranolol 40 mg/day achieved an HVPG response rate as high as 47% [15]. This showed that low-dose propranolol might be as effective as the target dose. In this study, a considerably high hemodynamic response rate was found for both propranolol 80 and 120 mg/day groups (50 vs. 54.1%) compared with the previous studies using target doses [7,8,11], which meant that the low dose was also effective. However, the response between the two groups was not significantly different and only 11.1% of cases achieved an additional hemodynamic response with propranolol at 120 mg/day among the nonresponders in the propranolol 80 mg/day group. This might indicate that the dose gradient does not always influence the response. However, this dose gradient led to a notable difference in the target heart rate (15.5 vs. 43.2%). This showed that the hemodynamic response was not consistent with the target dose. Propranolol at 120 mg/day led to a target heart rate of 43.2%; this may also mean that the average target dose might be slightly higher than 120 mg/day, which could be in agreement with the previous studies [8,11,20].

We carried out this study to show that propranolol 80 mg/day was as effective as propranolol 120 mg/day in the HVPG response, but had a much lower rate of adverse effects and discontinuation. This was well validated by the results. Six (30%) patients required discontinuation or reduction of dose; however, some of them did not achieve the target doses in the propranolol 120 mg/day group. In the propranolol 80 mg/day group, in only two (6.9%) patients was the dose reduced to 60 mg/day and there was

no discontinuation. This showed that propranolol 80 mg/day was safer and better tolerated than 120 mg/day. This was consistent with the fact that higher doses caused higher reduction and discontinuation. The safety and tolerance of different doses of propranolol were not reported in other low-dose studies; thus, it was unknown whether the patients could tolerate the doses well. This was also not reported in some target-dose studies [8,11]. In the real-world setting, the rate of discontinuation is high, and this may discourage patients and their physicians from using propranolol [9]. In other studies that targeted maximal tolerated doses, the discontinuations were up to 18–29% [14,20]; these included a large sample study involving 559 patients who used propranolol [13]. Our findings indicated the discontinuation and reduction of fixed-120 mg propranolol (43.2% of the target dose rate) up to 30%; this was in agreement with the previously mentioned studies.

Target heart rate is used widely to define the target dose in the administration of NSBBs. However, the decrease in heart rate was found not to be correlated with the HVPG response [10,14]. On the basis of this, does the target heart rate correlate with HVPG response? Does the target dose predict the HVPG response? If not, why should we adjust the dose of NSBBs on the basis of this because high doses had much lower safety and tolerance? To the best of our knowledge, these questions were answered in the previous studies. A new published retrospective study investigating different doses of carvedilol in HVPG response showed that both the relative change in pulse rate and heart rate response (falling $\geq 25\%$) were not associated with the HVPG response [21]. This was in line with our study. We carried out an analysis on the relationship between HVPG response and target dose. In the entire cohort, 51 (53.7%) patients were HVPG responders, whereas 29 (30.5%) patients achieved the target dose. The difference in the number of patients who achieved the target dose among responders and nonresponders was not significant ($P=0.800$). This result indicated that the target dose of propranolol was not related to the HVPG response, which was confirmed by the logistic regression analysis. Moreover, no independent predictors of HVPG response were identified in the logistic regression analysis. This result was in agreement with most previous studies [14,22] and not in agreement with some others [23].

There are some limitations to this study. First, the study was a single-center nonrandomized retrospective experience, and the sample size was small. Second, the doses used in this study were fixed at 80 and 120 mg/day; this did not represent the other doses including the maximal tolerated dose. For example, one study found that two of the six nonresponders for 40 mg responded at a dose of 160 mg/day [24]; however, the sample size in this study was too small. In the present study, setting a group with the target dose as a positive control showed more persuasive results. Despite this, our results were still consistent with the previous pivotal studies.

Conclusion

The results of the present study showed that there is no dose-dependent effect of propranolol from 80 to 120 mg/day in the hemodynamic response of cirrhotic patients with gastroesophageal varices. This indicated that a fixed low-dose propranolol dose below the target dose might

lead to a considerable hemodynamic response and is much safer and better tolerated, with a lower incidence of discontinuation. Moreover, there is no correlation between HVPG response and target dose. No predicting individual factors have been found to be associated with the hemodynamic response. Further randomized studies are needed to confirm these findings.

Acknowledgements

This work was supported by key projects from the Medical Science and technology development Foundation, Nanjing Department of Health, China (No. ZKX14017).

Conflicts of interest

There are no conflicts of interest.

References

- de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; 63:743–752.
- La Mura V, Abraldes JG, Raffa S, Retto O, Berzigotti A, Garcia-Pagan JC, *et al.* Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. *J Hepatol* 2009; 51:279–287.
- Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. *Hepatology* 2003; 37:902–908.
- Reiberger T, Ulbrich G, Ferlitsch A, Payer BA, Schwabl P, Pinter M, *et al.* Carvedilol for primary prophylaxis of variceal bleeding in cirrhotic patients with haemodynamic non-response to propranolol. *Gut* 2013; 62:1634–1641.
- Albillos A, Garcia-Pagan JC, Iborra J, Bandi JC, Cacho G, Perez-Paramo M, *et al.* Propranolol plus prazosin compared with propranolol plus isosorbide-5-mononitrate in the treatment of portal hypertension. *Gastroenterology* 1998; 115:116–123.
- Heeboll S, Villadsen GE, Aagaard NK, Gronbaek H, Vilstrup H, Keiding S. Propranolol treatment of portal hypertension in cirrhosis patients is better the higher the untreated pressure: a single-centre prospective experience. *Scand J Gastroenterol* 2013; 48:969–973.
- Turnes J, Garcia-Pagan JC, Abraldes JG, Hernandez-Guerra M, Dell'Era A, Bosch J. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. *Am J Gastroenterol* 2006; 101:506–512.
- Sharma P, Kumar A, Jha S, Mishra SR, Sharma BC, Sarin SK. The haemodynamic response to propranolol in cirrhosis with arterial hypertension: a comparative analysis with normotensive cirrhotic patients. *Aliment Pharmacol Ther* 2010; 32:105–112.
- Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology* 2007; 46:922–938.
- Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017; 65:310–335.
- Kim SG, Kim TY, Sohn JH, Um SH, Seo YS, Baik SK, *et al.* A randomized, multi-Center, open-label study to evaluate the efficacy of carvedilol vs. propranolol to reduce portal pressure in patients with liver cirrhosis. *Am J Gastroenterol* 2016; 111:1582–1590.
- D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999; 19:475–505.
- Bossen L, Krag A, Vilstrup H, Watson H, Jepsen P. Nonselective beta-blockers do not affect mortality in cirrhosis patients with ascites: post hoc analysis of three randomized controlled trials with 1198 patients. *Hepatology* 2016; 63:1968–1976.
- La Mura V, Abraldes JG, Raffa S, Retto O, Berzigotti A, Garcia-Pagan JC, *et al.* Prognostic value of acute hemodynamic response to i.v. propranolol in patients with cirrhosis and portal hypertension. *J Hepatol* 2009; 51:279–287.

- 15 Schepke M, Wiest R, Flacke S, Heller J, Stoffel-Wagner B, Herold T, *et al.* Irbesartan plus low-dose propranolol versus low-dose propranolol alone in cirrhosis: a placebo-controlled, double-blind study. *Am J Gastroenterol* 2008; 103:1152–1158.
- 16 Zhang F, Duan X, Zhang M, Li Z, He Q, Wang Y, *et al.* Influence of CYP2D6 and beta2-adrenergic receptor gene polymorphisms on the hemodynamic response to propranolol in Chinese Han patients with cirrhosis. *J Gastroenterol Hepatol* 2016; 31:829–834.
- 17 Bang UC, Benfield T, Hyldstrup L, Jensen JE, Bendtsen F. Effect of propranolol on survival in patients with decompensated cirrhosis: a nationwide study based Danish patient registers. *Liver Int* 2016; 36:1304–1312.
- 18 Madsen BS, Nielsen KF, Fiella AD, Krag A. Keep the sick from harm in spontaneous bacterial peritonitis: dose of beta blockers matters. *J Hepatol* 2016; 64:1455–1456.
- 19 Mookerjee RP, Pavesi M, Thomsen KL, Mehta G, Macnaughtan J, Bendtsen F, *et al.* Treatment with non-selective beta blockers is associated with reduced severity of systemic inflammation and improved survival of patients with acute-on-chronic liver failure. *J Hepatol* 2016; 64:574–582.
- 20 Sharma P, Kumar A, Sharma BC, Sarin SK. Early identification of haemodynamic response to pharmacotherapy is essential for primary prophylaxis of variceal bleeding in patients with 'high-risk' varices. *Aliment Pharmacol Ther* 2009; 30:48–60.
- 21 Schwarzer R, Kivaranovic D, Paternostro R, Mandorfer M, Reiberger T, Trauner M, *et al.* Carvedilol for reducing portal pressure in primary prophylaxis of variceal bleeding: a dose–response study. *Aliment Pharmacol Ther* 2018; 47:1162–1169.
- 22 Turnes J, Hernandez-Guerra M, Abrales JG, Bellot P, Oliva R, Garcia-Pagan JC, *et al.* Influence of beta-2 adrenergic receptor gene polymorphism on the hemodynamic response to propranolol in patients with cirrhosis. *Hepatology* 2006; 43:34–41.
- 23 De BK, Sen S, Biswas PK, Sengupta D, Biswas J, Santra A, *et al.* Propranolol in primary and secondary prophylaxis of variceal bleeding among cirrhotics in India: a hemodynamic evaluation. *Am J Gastroenterol* 2000; 95:2023–2028.
- 24 Garcia-Tsao G, Grace ND, Groszmann RJ, Conn HO, Bermann MM, Patrick MJ, *et al.* Short-term effects of propranolol on portal venous pressure. *Hepatology* 1986; 6:101–106.