


ORIGINAL ARTICLE

Changes in transient elastography in early cirrhotic patients after receiving nonselective B-blocker for primary variceal bleeding prophylaxis: Three-month follow up

Panida Piyachaturawat,^{*,†}  Sith Siramolpiwat,[‡] Kanokwan Sonsiri,[†] Pisit Tangkijvanich[§] and Sombat Treeprasertsuk^{*,†}

^{*}Department of Medicine, Faculty of Medicine, [†]Gastroenterology Unit, Faculty of Medicine, [§]Liver Research Unit, Faculty of Medicine, Chulalongkorn University, Bangkok and [‡]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Thammasat University, Pathumthani, Thailand

Key words

early cirrhotic, nonselective B-blocker, primary variceal bleeding prophylaxis, transient elastography.

Accepted for publication 7 May 2018.

Correspondence

Sombat Treeprasertsuk, Professor, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Rama 4 Road, Pathumwan District, Bangkok 10330, Thailand.
Email: battan5410@gmail.com

Part of the information has been presented at the APASL, The Liver Meeting 2017, held at Shanghai International Convention Center between 15 and 19 February 2017 in Shanghai, China, as an oral presentation.

Ethics approval and consent to participate:

This study was conducted according to the principles expressed in the Declaration of Helsinki and was approved by the Gastroenterological Association of Thailand. All data used in this study were deidentified and released for research purposes, and therefore, consent forms were not required. Research protocol was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University.

Consent for publication: Patient records or information were anonymized and deidentified for research purposes. Consent to publish each patient's data was not obtained.

Availability of data and materials: We provide our additional supporting files as shown in figures; however, we do not wish to share our data because the dataset is owned by the Faculty of Medicine, Chulalongkorn University, Thailand, which has a policy that strictly limits the use of this data to our specific objective only following Institutional Review Board (IRB) approval.

Competing interests: The authors declare that they have no competing interests, including financial competing interests and nonfinancial competing interests.

Abstract

Background and Aim: A nonselective B-blocker (NSBB) is recommended for primary prophylaxis of variceal bleeding. The impact of treatment with NSBB on modulating transient elastography (TE) has not been reported. The aim of the study is to investigate the effect of NSBB treatment on TE in early cirrhotic patients.

Methods: In this prospective study, we enrolled all early cirrhotic patients who underwent esophagogastroduodenoscopy (EGD) and showed small esophageal varices (EV) at our institute for a period of 1 year. The TE and heart rate (HR) of all participants were measured before and 3 months after receiving NSBB.

Results: Thirty-nine patients receiving propranolol for 3 months were analyzed. There were 16 patients in the HR responder group (41%) and 23 patients in the HR nonresponder group (59%). The reduction of TE was preferably found in the HR responder group compared with the HR nonresponder group, in which mean changes in TE were -5.6 and -0.7 kPa, respectively ($P = 0.23$). In addition, we categorized the patients using their TE responses. Twenty-five patients (64.1%) showed reduced TE during the follow-up period, in which the mean TE value change was -2.94 kPa. Using correlation analysis, TE and HR responses were insignificantly correlated ($r = 0.23$, $P = 0.15$).

Conclusion: The NSBB administered for 3 months mainly improved TE value in early cirrhotic patients even though the changes of HR and TE did not correlate. Further study is needed to confirm whether the monitoring of TE change may be a better predictor for pharmacological response than the HR response.

Author contribution: PP proposed the study concept and design as well as interpreted the data and edited the manuscript; KS coordinated the research and keyed in data; SS and PT provided suggestions for the study concept and critically revised the manuscript; and ST interpreted the data, edited, and critically revised the manuscript.

Funding: This research study was supported by grants from the Gastroenterological Association of Thailand (GAT), Research Fund and Liver Research Unit of Faculty of Medicine, Chulalongkorn University, and a research presentation grant from the Fatty Liver Unit, Division of Gastroenterology, Chulalongkorn University, Bangkok, Thailand.

Introduction

Portal hypertension (PHT) is a pathological increase in portal venous pressure. This increase causes several complications, particularly upper gastrointestinal bleeding resulting from ruptured gastroesophageal varices. In cirrhotic patients with esophageal varices (EV), the incidence of first variceal bleeding is about 12–15% per year.^{1–3} In the past decade, several studies demonstrated promising medications that decrease portal pressure, and one of them was a nonselective B-blocker (NSBB).^{4–13} The most commonly used guidelines for the management of PHT (AASLD 2007, Baveno VI) recommended the use of NSBB for primary and secondary prophylaxis of variceal bleeding.^{14,15} However, the effectiveness of NSBB treatment depends on it achieving a reduction in the portal pressure of individuals.

The hepatic venous pressure gradient (HVPG) is a standard surrogate marker of portal pressure measurement to diagnose and assess the severity of PHT as well as monitor the hemodynamic response in patients after receiving NSBB.^{16–19} However, HVPG is an invasive procedure and is inapplicable due to its high cost. Recently, a noninvasive method, transient elastography (TE), has become one acceptable tool to assess liver fibrosis.²⁰ Recent studies have also demonstrated a significant correlation of TE and HVPG, especially in patients with early cirrhosis,^{20–22} such as Reiberger's study, which suggested that early cirrhotic patients had a linear correlation of HVPG and TE and became stronger under treatment with NSBB ($r = 0.93$, $P < 0.0001$).²³ The results of TE measurements are influenced by several factors, including level of aminotransferases, cause of chronic liver disease, body mass index (BMI), fasting state, and patient position.²⁴ Nevertheless, TE has been used across the world in clinical practice due to its convenient follow up and cost effectiveness. As there is no report on the dynamic changes of TE under the effect of NSBB, we aimed to evaluate the impact of treatment with NSBB on TE changes and the correlation of TE and heart rate (HR) responses.

Materials and methods

Patients. Data were collected prospectively from April 2015 to February 2016. A total of 42 early cirrhotic patients underwent endoscopy for variceal surveillance at King Chulalongkorn

Memorial Hospital (KCMH), Thailand, and informed consent was obtained. All patients who had small EV and who were receiving NSBB with propranolol for primary prophylaxis of variceal bleeding were included. Patients who received an NSBB prior to the study date and those who had stopped medication for more than 3 months before enrollment were also included. Patients of both genders with contraindications or those with serious adverse effects of NSBB, BMI >30 kg/m², history of alcohol consumption more than 70 g/wk in women and 140 g/wk in men within 6 months; cirrhotic patients with Child-Turcotte-Pugh C (CTP score > 10); and imaging evidence of liver mass were excluded from this study.

A complete medical history, including etiology of liver disease and HR measurement, was taken prior to TE for all patients. Laboratory evaluations including liver biochemistries (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] level, albumin, and total bilirubin), creatinine, complete blood count, and metabolic profile (fasting glucose, total and HDL cholesterol, and triglycerides) were recorded. Demographic and anthropometric data, including age, gender, body weight, height, BMI, and CTP scores, were calculated. The study was approved by the institutional review board.

HR measurement. The HRs of all patients were measured thrice with at least 5 min in the sitting position prior to each measurement. Average resting HRs were then calculated and recorded.

TE measurement. TE was performed using Fibroscan (Echosens, Paris, France) by a scientist (KS) who was experienced in TE measurement (>500 cases/year) after a 2-h period of fasting. The tip of an ultrasound probe was placed in an intercostal space on the right lobe of the liver with the patient lying in dorsal decubitus position and the right arm in maximal abduction. Vibrations of a mild amplitude and low frequency were transmitted to the liver tissue. The velocity of the induced shear wave is directly related to liver stiffness. The measurement of liver stiffness was considered adequate if a total of 10 validated measurements were obtained with a 60% success rate. The results of the median value and interquartile range were recorded in kilopascal (kPa) as a standard recommendation.^{25,26}

Protocol for medical prophylaxis of variceal bleeding. After the measurement of TE at baseline, an NSBB (propranolol) was initiated and was increased stepwise (monthly) until systolic blood pressure (SBP) was maintained at >90 mmHg, and the HR was at least 50/min. The maximum target dose for propranolol was 80 mg/day (40 mg bid). The TE and HR responses to NSBB were assessed again at 3 months after taking propranolol. An HR responder was defined as patients who had HR reduction of at least 25% compared to baseline.¹⁴

Methods. TE and HR measurement were performed in all patients at baseline and 3 months after taking propranolol. Patients were followed up on a monthly basis, and doses of propranolol were adjusted according to the protocol and monitored for adverse events. Absolute TE change (kPa) and %TE change $[(TE_2 - TE_1)/TE_1 \times 100]$ were calculated.

Study definitions. HR responder is defined as a person who had an HR of 50–55 beats/min or an HR reduced >25% from baseline, and SBP was more than 90 mmHg.

HR nonresponder is defined as a person whose HR was not reduced as above after adjusting the maximal or tolerated doses of NSBB.

TE responder is defined as a person whose TE is reduced during the 3-month follow-up period.

TE nonresponder is defined as a person whose TE is increased or has not changed during the 3-month follow-up period.

Sample size. The sample size necessary for correlation was calculated to determine a relationship between the HR and TE responses. The sample size calculation, which was based on correlation coefficient ($r = 0.5$), was 39 patients.

Statistical analysis. All statistical analyses were performed using SPSS software (version 22; SPSS Inc., Chicago, IL, USA). Clinical and laboratory characteristics of patients were expressed as the mean \pm standard deviation (SD). Non-normally distributed variables, such as median and range, were assessed using Student's *t*-test and nonparametric test, respectively. The Chi-square test was used to evaluate the association between categorical variables and liver fibrosis. Differences between groups were analyzed by a two-tail independent *t*-test. A *P*-value less than 0.05 was considered statistically significant. The correlations of TE change and HR response were analyzed using point biserial correlation.

Results

A total of 42 patients with small EV were included and underwent TE measurements. During the study period, three patients were excluded because one patient developed hepatocellular carcinoma (HCC), and two patients were lost to follow up. Thus, 39 patients were finally included (Figure 1).

The mean age of cirrhotic patients was 58.1 ± 10.6 years, and 59% ($n = 23$) of them were male. Twenty patients (51.3%) demonstrated impaired fasting blood glucose or diabetes mellitus (DM). The major causes of cirrhosis were hepatitis C and

hepatitis B infections. The median time interval between the first and second TE was 90 ± 7 days. All patients were treated with propranolol. We divided the 39 patients into two groups; the HR responder group ($n = 16$, 41%) and the HR nonresponder group ($n = 23$, 59%). The etiologies of cirrhosis, baseline characteristics, and level of aminotransferases were not different between the two groups.

Baseline TE of the HR responder and HR nonresponder groups were $24.7 (\pm 14)$ and $20.9 (\pm 8)$ kPa ($P = 0.32$), respectively, whereas the second TE, which was performed 3 months after taking NSBB, were $19.7 (\pm 12)$ and $16 (\pm 9)$ kPa ($P = 0.93$), respectively. The mean changes in TE were -5.6 kPa in the HR responder and -0.7 kPa in the HR nonresponder group ($P = 0.23$). The percent changes of TE $[(TE_2 - TE_1)/TE_1 \times 100]$ were -0.19% and -0.06% ($P = 0.15$), respectively (Table 1).

In addition, we categorized cirrhotic patients into two groups by TE response, as shown in Table 2. There were 25 (64.1%) patients who showed reduced TE during the 3-month follow-up period. The mean TE value change was -2.94 kPa, and the HR response was 48% ($n = 12$) in this group.

Between the two HR groups, the percentage of TE change was not significantly different (Table 2). Using point biserial

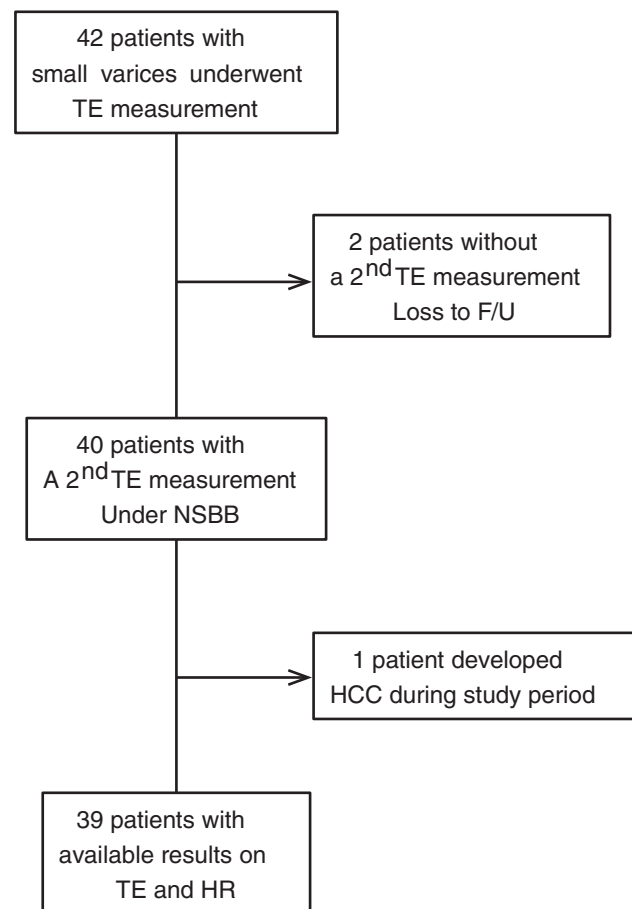


Figure 1 Patient enrollment flowchart: 42 patients underwent transient elastography (TE) measurements.

Table 1 Baseline characteristic data of 39 cirrhotic patients

Characteristics	Total (N = 39)	HR responder (N = 16, 41%)	HR nonresponder (N = 23, 59%)	P-value
Age, years	58.1 (10.6)	57.4 (12.8)	58.6 (9.0)	0.52 ⁺
Male gender, n (%)	23 (59)	8 (50.0)	15 (65.2)	0.34 [‡]
BMI, kg/m ²	24.3 (3.3)	23.9 (3.2)	24.4 (3.5)	0.73 ⁺
BMI ≥ 25 kg/m ² , n (%)	14 (35.9)	5 (31.3)	9 (39.1)	0.61 [‡]
IFG/DM, n (%)	20 (51)	7 (43.8)	13 (56.5)	0.43 [‡]
ALT, IU/L	32 (23.8)	31.5 (27.8)	34.5 (21.1)	0.94 [§]
AST/ALT ratio	1.4 (0.5)	1.4 (0.3)	1.5 (0.6)	0.07 ⁺
ALP, IU/L	98 (59.2)	107.0 (82.6)	96.5 (36.7)	0.90 [§]
Albumin, g/L	3.7 (0.5)	3.6 (0.6)	3.7 (0.5)	0.12 ⁺
Platelet ×10 ⁹ , L	120 (45)	102 (45)	138 (45)	0.17 [§]
INR	1.15 (0.2)	1.17 (0.29)	1.17 (0.11)	0.27 ⁺
Creatinine, mg/dL	0.84 (0.23)	0.84 (0.18)	0.84 (0.27)	0.34 ⁺
Etiology, n (%)				
Hepatitis C	10 (26)	5 (31.3)	5 (21.7)	Note [§] : cryptogenic AIH
Hepatitis B	10 (26)	5 (31.3)	5 (21.7)	
Alcoholic liver	11 (28)	4 (25)	7 (30.4)	
Nonalcoholic steatohepatitis	2 (5)	0 (0)	2 (8.7)	
Others [§]	6 (15)	2 (12.5)	4 (17.4)	
CTP-A	27 (69)	10 (62.5)	17 (73.9)	
CTP-B	12 (31)	6 (37.5)	6 (26.1)	
Average BW change (BW2-BW1), kg	0.1 (1.2)	-0.1 (0.8)	0.2 (1.4)	0.59 [§]
TE at baseline (IQR), kPa	21.3 (11)	24.7 (14)	20.9 (8)	0.32 [§]
Heart rate at baseline, /min	80 (11)	75 (9)	80 (11)	0.08 [§]
TE at 3 months of follow up (IQR), kPa	17.1 (11)	19.7 (12)	16 (9)	0.93 [§]
TE change (TE2-TE1), kPa	-1.0	-5.6	-0.7	0.23 [§]
%TE change	-0.07	-0.19	-0.06	0.15 [§]

BMI, body mass index; BW, body weight; CTP, child-turcotte-pugh; DM, diabetes mellitus; HR, heart rate; IQR, interquartile range. ⁺Student *t* test. [‡] χ^2 test. [§]Mann-Whitney test.

correlation analysis, the TE and HR were not correlated ($r = 0.23$, $P = 0.15$) (Figure 2).

During the 3-month follow-up period, no serious adverse events occurred from taking NSBB. All 39 patients, whose pill count was monitored, had good adherence and compliance.

Discussion

The main therapeutic effect of NSBBs on liver cirrhotic patients is mediated through the hemodynamic alterations, such as

Table 2 Comparison according to transient elastography measurement value change

Characteristics	Reduced TE (N = 25)	No change or Increased TE (N = 14)	P-value
TE at baseline (IQR), kPa	22.8 (12)	20.3 (9)	0.52
Heart rate, /min	81 (2)	77 (3)	0.22
HR response, n (%)	12 (48)	4 (28.6)	0.23
TE change (TE2-TE1), kPa	-2.94	+5.25	0.02

HR, heart rate; TE, transient elastography.

lowering the portal pressure and reducing the risk of variceal bleeding. To date, there is no study on the dynamic changes of TE in cirrhotic patients taking NSBB compared to HR response,

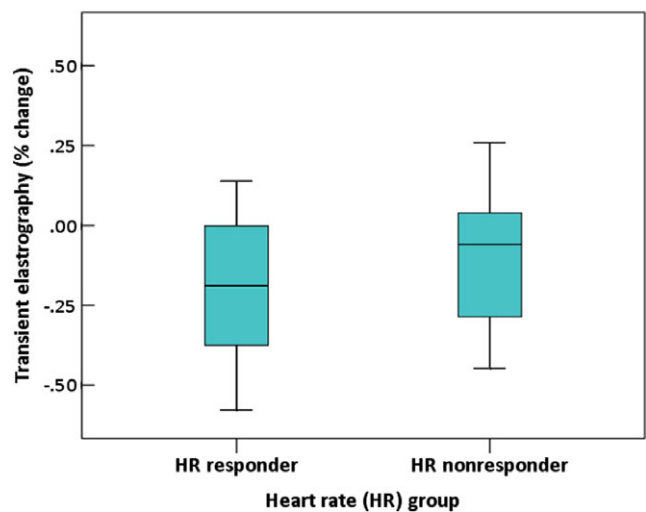


Figure 2 A correlation of transient elastography (TE) change and heart rate response that was analyzed using point biserial correlation and showed poor correlation (coefficient $r = 0.23$, $P = 0.15$).

which is commonly used in clinical practice. In the present study, we evaluated the change of TE in early cirrhotic patients after receiving propranolol (NSBB) therapy for 3 months, and we demonstrated a trend of reduction of the TE in early cirrhotic patients after the treatment. The improvement of TE was preferably found in HR responder patients. However, many HR nonresponders showed TE improvement, suggesting the benefit of NSBB in HR nonresponders.

There was no correlation of TE change with HR in early cirrhotic patients after receiving NSBB. This finding was consistent with the earlier report by Garcia-Tsao *et al.*,⁴ who investigated the effect of propranolol on portal pressure determined by the HVPG in alcoholic cirrhotic patients. Of the patients who were defined as “responder,” 60% were found to have reduced HVPG > 10% after administration of propranolol. In the comparison between responder and nonresponder groups, these investigators showed that a reduction in HR did not correlate with the reduction in HVPG.⁴ Neither the HR response to propranolol nor the propranolol plasma concentration could be used to assess the portal pressure response. In the current guidelines for management of portal hypertension (American Association for the Study of Liver Diseases [AASLD] 2007, Baveno VI), NSBB is recommended for primary and secondary prophylaxis of variceal bleeding.^{14,15} Due to the invasiveness of HVPG measurement, the recommended dose of B-blockers should be titrated to the goal of reduction of the HR by 25% from baseline or adjusted to maximal tolerated doses.^{14,15}

In the present study, we also noticed a decline in TE after NSBB in about 64% of patients. It was similar to the HVPG responders in the earlier study, which showed declined HVPG in 60% of alcoholic cirrhotic patients after propranolol administration. As HVPG is not available in this study, it is not clear whether the decline in TE value can be used as a hemodynamic response, such as HVPG. However, Reiberger *et al.*²³ demonstrated a strong correlation between TE and HVPG. By analogy, the reduction of TE may implicate the reduction of HVPG.

Regarding the TE change in TE responders, we found a reduction of TE of 2.94 kPa within 3 months after NSBB treatment that was demonstrated in 64% of our patients. TE value was measured using two components: structural (parenchymal) and functional (vascular) components. Several factors, including level of aminotransferases, cause of chronic liver disease, BMI, fasting state, and patient position, influence the results of TE measurements.²⁴ From our study criteria, we enrolled patients who were in the early stages of chronic liver disease, which included 52% with inactive hepatitis C and hepatitis B infections and inactive alcoholic drinking (at least 6 months without alcohol), NASH patients with average body weight change at 0.1 kg, and patients who did not have ascites or were obese. Thus, we presumed that the TE value change of approximately 3 kPa in 3 months demonstrated in our patients may be a consequence of the improvement of the dynamic components, which reflects vascular changes under the propranolol effect. In addition to lower the HR, the hemodynamic effect of propranolol involved several other activities, including a decrease in cardiac output via B1 receptors, reduction of portal inflow by causing vasoconstriction of splanchnic area, and reduction of variceal flow.²⁷ However, further studies are required to investigate the potential hemodynamic benefit effect of NSBB in our early cirrhotic patients.

There are several limitations that warrant careful interpretation of this study. First, the follow-up time is 3 months, even if there was a report from Villanueva *et al.*, who demonstrated that acute hemodynamic response to beta-blockers could be used to predict the long-term risk of first bleeding,²⁸ and a long-term follow up is recommended. Second, we could not perform the HVPG, the gold-standard measurement of portal pressure, due to its high procedural cost. We are aware of the interpretation of our study. Nevertheless, HVPG is not the end result of NSBB prophylaxis. The presence of EVs or clinical PHT is a major outcome goal during follow up. Third, we categorized patients as HR responders or HR nonresponders, which is measured in real-life practice and is not the effect of real portal hemodynamic response, but the HR response was generally used in clinical practice. Fourth, our sample size was precisely calculated to determine the correlation between TE and HR change, but the number was not enough to determine the relationship between HR responder and TE responder. Fifth, the maximum target dose of NSBB in our study was only 80 mg/day. In theory, the maximum target dose of NSBB was 160 mg/day, but in clinical practice, most of enrolled patients can only tolerate a maximum amount of 80 mg/day.

In conclusion, our study showed the improvement of TE in early cirrhotic patients under 3 months of NSBB therapy. If adequately validated, this information may be useful for making a decision of using NSBB therapy in these early cirrhotic patients. Further study is needed to confirm that the monitoring of TE change may be a better predictor for pharmacological response than the HR response.

Acknowledgments

We thank the following organization for grant support: the Gastroenterological Association of Thailand (GAT), Research Fund, the Liver Research Unit of the Faculty of Medicine, Chulalongkorn University, as well as the Fatty Liver Unit, Division of Gastroenterology. We also thank Pornthip Sinthavanuruk and Sranya Phaisawang, Research affairs, Chulalongkorn University, Bangkok, Thailand, for their support in English editing.

References

- Graham DY, Smith JL. The course of patients after variceal hemorrhage. *Gastroenterology*. 1981; **80**: 800–9.
- Gores GJ, Wiesner RH, Dickson ER, Zinsmeister AR, Jorgensen RA, Langworthy A. Prospective evaluation of esophageal varices in primary biliary cirrhosis: development, natural history, and influence on survival. *Gastroenterology*. 1989; **96**: 1552–9.
- D’Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *J. Hepatol*. 2006; **44**: 217–31.
- Garcia-Tsao G, Grace ND, Groszmann RJ *et al.* Short-term effects of propranolol on portal venous pressure. *Hepatology*. 1986; **6**: 101–6.
- Groszmann RJ, Bosch J, Grace ND *et al.* Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. *Gastroenterology*. 1990; **99**: 1401–7.
- Pagliaro L, D’Amico G, Sorensen TI *et al.* Prevention of first bleeding in cirrhosis. a meta-analysis of randomized trials of nonsurgical treatment. *Ann. Intern. Med.* 1992; **117**: 59–70.

- 7 D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology*. 1995; **22**: 332–54.
- 8 Bernard B, Lebrech D, Mathurin P, Opolon P, Poynard T. Beta-adrenergic antagonists in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *Hepatology*. 1997; **25**: 63–70.
- 9 Cales P, Oberti F, Payen JL *et al.* Lack of effect of propranolol in the prevention of large oesophageal varices in patients with cirrhosis: a randomized trial. French-Speaking Club for the Study of Portal Hypertension. *Eur. J. Gastroenterol. Hepatol.* 1999; **11**: 741–5.
- 10 D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin. Liver Dis.* 1999; **19**: 475–505.
- 11 Garcia-Pagan JC, Escorsell A, Moitinho E, Bosch J. Influence of pharmacological agents on portal hemodynamics: basis for its use in the treatment of portal hypertension. *Semin. Liver Dis.* 1999; **19**: 427–38.
- 12 Merkel C, Marin R, Angeli P *et al.* A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis. *Gastroenterology*. 2004; **127**: 476–84.
- 13 Giannelli V, Lattanzi B, Thalheimer U, Merli M. Beta-blockers in liver cirrhosis. *Ann Gastroenterol.* 2014; **27**: 20–6.
- 14 Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W, the Practice Guidelines Committee of the American Association for the Study of Liver Diseases and the Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007; **46**: 922–38.
- 15 de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J. Hepatol.* 2015; **63**: 743–52.
- 16 Perello A, Escorsell A, Bru C *et al.* Wedged hepatic venous pressure adequately reflects portal pressure in hepatitis C virus-related cirrhosis. *Hepatology*. 1999; **30**: 1393–7.
- 17 Thalheimer U, Leandro G, Samonakis DN, Triantos CK, Patch D, Burroughs AK. Assessment of the agreement between wedge hepatic vein pressure and portal vein pressure in cirrhotic patients. *Digest. Liver Dis.* 2005; **37**: 601–8.
- 18 D'Amico G, Garcia-Pagan JC, Luca A, Bosch J. Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review. *Gastroenterology*. 2006; **131**: 1611–24.
- 19 Bosch J, Abralde JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nat. Rev. Gastroenterol. Hepatol.* 2009; **6**: 573–82.
- 20 Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. *J. Hepatol.* 2012; **56**: 696–703.
- 21 Robic MA, Procopet B, Metivier S *et al.* Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. *J. Hepatol.* 2011; **55**: 1017–24.
- 22 Procopet B, Tantau M, Bureau C. Are there any alternative methods to hepatic venous pressure gradient in portal hypertension assessment? *J. Gastrointest. Liver Dis.* 2013; **22**: 73–8.
- 23 Reiberger T, Ferlitsch A, Payer BA *et al.* Non-selective beta-blockers improve the correlation of liver stiffness and portal pressure in advanced cirrhosis. *J. Gastroenterol.* 2012; **47**: 561–8.
- 24 Castera L, Foucher J, Bernard PH *et al.* Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology*. 2010; **51**: 828–35.
- 25 Sandrin L, Fourquet B, Hasquenoph JM *et al.* Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med. Biol.* 2003; **29**: 1705–13.
- 26 Castera L, Forns X, Alberti A. Non-invasive evaluation of liver fibrosis using transient elastography. *J. Hepatol.* 2008; **48**: 835–47.
- 27 Mandorfer M, Reiberger T. Beta blockers and cirrhosis, 2016. *Digest. Liver Dis.* 2017; **49**: 3–10.
- 28 Villanueva C, Aracil C, Colomo A *et al.* Acute hemodynamic response to beta-blockers and prediction of long-term outcome in primary prophylaxis of variceal bleeding. *Gastroenterology*. 2009; **137**: 119–28.