Hemodynamic Response to Carvedilol is Maintained for Long Periods and Leads to Better Clinical Outcome in Cirrhosis: A Prospective Study

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Background: Non-selective beta-blockers (NSBBs), e.g. propranolol, are recommended for prophylaxis of variceal bleeding in cirrhosis. Carvedilol, a newer NSBB with additional anti- α_1 -adrenergic activity, is superior to propranolol in reducing portal pressure. Repeated HVPG measurements are required to identify responders to NSBB. We aimed to determine whether a single-time HVPG measurement, using acute-hemodynamic-response-testing, is sufficient to predict long-term response to carvedilol, and whether these responders have better clinical outcome. **Methods:** Consecutive patients with cirrhosis, aged 18–70 years, in whom NSBB was indicated for primary/secondary prophylaxis of variceal bleeding, and who underwent HVPG were included. Acute-hemodynamic-response was defined as a decrease in HVPG $\geq 10\%$ from baseline or absolute HVPG value declining to <12 mm Hg, 1 h after 25 mg oral carvedilol. The aims of the study were to determine: the proportion of patients who achieved acute-hemodynamic-response to carvedilol; whether HVPG-response is maintained for 6 months; and clinical outcome of acute-responders to carvedilol therapy for 6 months. **Results:** The study included 69 patients (median age 51, males 93%). Alcohol was the most common etiology; 59% patients belonged to Child-Pugh class B. NSBB was indicated for primary prophylaxis in 36% and secondary prophylaxis in 64% patients. According to the response criteria, 67% patients were found to be acute-hemodynamic-responders. At 6 months, 92% patients were found to be still maintaining their hemodynamic response to carvedilol. Using intention-to-treat analysis, 76% patients maintained their response. These acute responders, on chronic treatment with carvedilol during the 6-month period, had lesser episodes of variceal bleeding, better ascites control, and improved MELD and CTP scores, than non-carvedilol treated non-responders. However, survival remained similar in both the groups. **Conclusions:** A single-time HVPG measurement with acute-hemodynamic-response-testing is simple and reliable method for identifying patients who are more likely to respond to carvedilol therapy. The HVPG-response is maintained over a long period in majority of these patients and carvedilol therapy leads to better clinical outcome in these patients. (J CLIN EXP HEPATOL 2016;6:175–185)

Portal hypertension is responsible for most and often lethal complications of cirrhosis such as bleeding from esophagogastric varices, ascites, renal dysfunction, and hepatic encephalopathy. Because of the combined impact of these complications, portal hypertension remains the most important cause of morbidity and mortality in patients with cirrhosis.¹ A decrease in portal pressure is not only protective against the risk of

variceal bleeding but is also associated with a lower long-term risk of developing complications and an improved long-term survival. A milestone in therapy was the introduction of non-selective beta-blockers (NSBBs) for the prophylaxis of variceal bleeding. However, in practice, less than 50% of patients are hemodynamic responders to traditional NSBBs such as propranolol or nadolol.¹ Carvedilol is a new NSBB with an additional property of vasodilatation due to its intrinsic anti- α_1 adrenergic activity and its capacity to enhance the release of nitric oxide.^{2,3} Thus, carvedilol is a more potent agent than other NSBB in reducing portal pressure and is likely to be effective in more patients.

The gold standard method to know whether a patient is a responder to NSBB is to measure the HVPG at baseline, and then repeat HVPG measurement after chronic administration of NSBB. However, concerns have been raised in relation to the feasibility, the clinical appropriateness, the risks, and the costs of repeated HVPG measurement.^{4,3} Acute-hemodynamic-response-testing is a technique in which HVPG is repeated at 60–90 min after oral or

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Abbreviations: CTP: Child-Turcotte-Pugh; EVL: endoscopic variceal ligation; FHVP: free hepatic venous pressure; HVPG: hepatic venous pressure gradient; MELD: model for end-stage liver disease; NSBB: non-selective beta-blocker; VBL: variceal band ligation; WHVP: wedged hepatic venous pressure

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intravenous NSBB being tested. Many studies have investigated the role of acute HVPg response to intravenous or oral propranolol in predicting the risk of bleeding and survival.⁵⁻⁹ We aimed to determine whether a single-time HVPg measurement, using acute-hemodynamic-response-testing, is sufficient to predict long-term response to carvedilol, and whether these responders have better clinical outcome.

PATIENTS AND METHODS

Patients

This was a prospective study conducted in the Department of Gastroenterology at Sir Ganga Ram Hospital, New Delhi, India, between August 2011 and May 2013. The ethics committee of the hospital approved the study and a written informed consent was obtained from all the participants. The study conformed to the Helsinki declaration of 1975 as revised in 1983.

Inclusion Criteria

All consecutive patients of cirrhosis, between ages 18 and 70 years, in whom NSBB was indicated for primary or secondary prophylaxis (i.e. patients with large [>5 mm] esophageal varices¹⁰ or those with varices of any size but with history of variceal bleeding), and who consented to undergo HVPg, were enrolled. The diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonographic data or histology if available.

Exclusion Criteria

(i) Patients already on NSBBs at the time of HVPg; (ii) concomitant HIV infection; (iii) associated severe cardiac or pulmonary co-morbidities; (iv) renal dysfunction (serum creatinine >1.6 mg/dL); (v) grade 3-4 hepatic encephalopathy at the time of enrollment; (vi) hepatocellular carcinoma or other malignancies; (vii) underwent shunt surgery or TIPSS for portal hypertension; (viii) pregnancy; (ix) systolic blood pressure <90 mm Hg at the time of HVPg; and (x) failure to give consent for inclusion in the study.

The baseline clinical and laboratory parameters were recorded in all the included patients.

Aims of the Study

Primary Aim

To determine the proportion of patients who have acute-hemodynamic-response to carvedilol.

Secondary Aims

(i) To assess whether acute-hemodynamic-response is maintained for long-term (6 months); and (ii) to assess whether carvedilol therapy leads to a better clinical outcome in patients who were acute-hemodynamic-responders compared to non-carvedilol treated patients who were

not acute-hemodynamic-responders (i.e. acute-hemodynamic-non-responders).

HVPg

HVPg measurement was done after overnight fast, using the standard technique.^{11,12} If the patient was on any portal pressure reducing drug, it was stopped prior to HVPg measurement as per following schedule: Beta-blocker was stopped for at least 7 d; terlipressin was stopped for at least 24 h; and somatostatin was stopped for at least 12 h. Under local anesthesia, a 7F vascular sheath (Arrow Medical, Athens, TX, USA) was placed in the right femoral vein or internal jugular vein using the Seldinger technique. HVPg was measured by the standard technique^{11,12} in which a balloon catheter was introduced into the middle or right hepatic vein under fluoroscopic guidance. Atmospheric pressure at the level of mid-axillary line was set as the zero reference point. The free hepatic venous pressure (FHVP) was obtained by keeping the catheter free into the lumen of the hepatic vein. The balloon of the catheter was then inflated to wedge the lumen of hepatic vein and pressure recorded. Presence of wedging was confirmed by absence of reflux into the inferior vena cava, after injection of 2 ml intravenous contrast, and appearance of a sinusoidogram. The pressure tracing at this juncture was labeled as wedged hepatic venous pressure (WHVP). HVPg was determined by subtracting free from wedged hepatic venous pressures (WHVP – FHVP). WHVP and FHVP readings were repeated several times (at least thrice) and average value was taken. If the difference between the two HVPg readings was more than 1 mm Hg, all the readings were discarded and fresh set of measurements were taken. The normal accepted value for HVPg is 1-5 mm Hg.

After taking the baseline HVPg reading, the patient was given 25 mg of carvedilol orally, on table. A repeat HVPg measurement was done 1 h after giving carvedilol. The post carvedilol HVPg value was compared with the baseline HVPg value. On the basis of HVPg response to carvedilol, patients were classified as:

- *Acute-hemodynamic-responders*: Fall in HVPg $\geq 10\%$ from baseline or absolute HVPg value declining to <12 mm Hg.
- *Acute-hemodynamic-non-responders*: Not satisfying above criteria.

Treatment and Follow-Up

All the acute-hemodynamic-responders were started on carvedilol at a dose of 12.5 mg/d (in two divided doses), in addition to the standard endoscopic therapy (endoscopic variceal ligation for esophageal varices and cyanoacrylate glue for gastric varices). Patients who were acute-hemodynamic-non-responders received standard endoscopic therapy alone.

All patients were followed for 6 months and were monitored at regular intervals for complications of cirrhosis (variceal bleeding, ascites, hepatic encephalopathy, etc.)

Figure 1 Study design.

and adverse effects to therapy. Patients also received standard medical care depending on their clinical status and etiology. Abstinence was advised to the alcoholic patients. In case of any hospitalization during the follow-up period, the patients were subjected to relevant investigations as required and received treatment as indicated. At the end of follow-up, HVPG was done again in acute-hemodynamic-responders and the value was compared with their respective baseline value to see whether their HVPG-responder status was still maintained. Acute-hemodynamic-non-responders were not subjected to any repeat HVPG at 6 months. The study design is shown in Figure 1.

Sample Size Calculation

Assuming the acute-hemodynamic-response rate of 60% based on previous study,¹³ precision level of 10%, and confidence level of 90%, it was estimated that we needed a sample size of 65 patients. We included 69 patients in our study.

Statistical Analysis

Quantitative data were expressed as median (range) and compared using Mann Whitney *U* test or Wilcoxon signed-rank test. Qualitative data were expressed as number (%) and compared using Fisher's exact test or Pearson chi-square test. *P* value <0.05 was considered significant. Apart from the main outcome analysis for the whole group, a subgroup analysis for variceal bleeding, stratified according to primary and secondary prophylaxis, was also done.

Statistical analysis was conducted using the SPSS 17.0 statistical package (SPSS Inc, Chicago, IL, USA).

RESULTS

Patients

Between August 2011 and December 2012, a total of 80 patients, in whom NSBB was indicated, were enrolled for the study. Eleven patients were excluded for following reasons: (i) Already on NSBBs at the time of HVPG ($n = 6$); (ii) grade 3–4 hepatic encephalopathy at the time of enrollment ($n = 3$); and (iii) systolic blood pressure <90 mm Hg at the time of HVPG ($n = 2$). Hence, remaining 69 patients were included in the study. The last included patient was followed till May 2013.

The baseline characteristics of the patients are shown in Table 1. Most patients were middle-aged males and alcohol was the most common etiology of cirrhosis. Three patients also had alcoholic hepatitis, and their last alcoholic drink was 3–4 weeks ago, while other alcoholic patients were abstinent for a minimum of 2 months. Most patients belonged to Child class B and 61% of patients had ascites. NSBB was indicated for primary prophylaxis in 25/69 (36%) patients and for secondary prophylaxis in 44/69 (64%) patients.

Acute-Hemodynamic-Response-Testing

All 69 included patients underwent HVPG measurement successfully, including acute hemodynamic response testing. The baseline and one-hour post-carvedilol hemodynamic parameters are shown in Table 2. The median baseline HVPG value was 19 mm Hg (range 13–30 mm Hg). After carvedilol, there was a median 13% reduction in HVPG. The median post-carvedilol HVPG was 16.5 mm Hg (range 10–26 mm Hg). The cause of HVPG reduction was reduction in WHVP, while FHVP remained same after carvedilol. There was also statistically significant reduction in heart rate and mean arterial pressure. However, the mean arterial pressure did not drop below 60 mm Hg in any of the patients. According to the response criteria, 46/69 (67%) patients were found to be acute-hemodynamic-responders while 23/69 (33%) patients were found to be acute-hemodynamic-non-responders. In responders, the HVPG reduced by a median of 20%.

Predictors of Acute-Hemodynamic-Response

Baseline factors were compared between acute-hemodynamic-responders and acute-hemodynamic-non-responders as shown in Table 3. On univariate analysis, serum creatinine was the only factor significantly different between the two groups. In acute-hemodynamic-responder group, the median baseline serum creatinine was 0.8 (range 0.4–1.6) mg/dL, which was significantly lesser than serum creatinine of acute-hemodynamic-non-responder group,

Table 1 Baseline Characteristics of Included Patients.

Parameter	Value (n = 69)	
Age (years)	51	(26–74)
Sex		
Males	64	(93%)
Females	5	(7%)
Etiology of cirrhosis		
Alcohol	41	(59%)
NASH or cryptogenic	19	(28%)
Viral	9	(13%)
MELD	13	(6–32)
CTP score	8	(5–13)
Child-Pugh class		
A	16	(23%)
B	41	(59%)
C	12	(17%)
Ascites present	42	(61%)
HE (grade 1–2) present	3	(4%)
History of variceal bleeding	44	(64%)
Transient elastography (kPa) (n = 41)	50.5	(13.9–75.0)
Esophageal varices		
Small	27	(39%)
Large	42	(61%)
Associated gastric varices present	14	(20%)
PHG present	17	(25%)
Hemoglobin (g/dL)	9.3	(6.9–17.0)
Platelets, $n \times 10^3/\text{mm}^3$	102	(13–462)
Creatinine (mg/dL)	0.9	(0.4–1.6)
Sodium (meq/dL)	134	(103–147)
Potassium (meq/dL)	3.9	(3.1–5.3)
Bilirubin (mg/dL)	1.7	(0.4–20.9)
Albumin (g/dL)	2.8	(1.6–4.3)
INR	1.4	(1.0–3.6)

which was 1.0 (range 0.7–1.6) mg/dL. In addition, in acute-hemodynamic-responder group, the baseline serum sodium and HVPg values were also marginally (though not significantly) higher than these values in acute-hemodynamic-non-responder group (*P* value 0.074 for each). When creatinine, sodium, and HVPg values were entered into multivariate analysis, serum creatinine and HVPg were found to be independently associated with acute-hemodynamic-response (odds ratio (95% CI): 0.036 (0.002, 0.530) for creatinine and 1.310 (1.066, 1.611) for HVPg).

HVPg at 6 Months

Patients with acute-hemodynamic-response (*n* = 46) received carvedilol at a dose of 12.5 mg/d till the end of the study. A repeat HVPg assessment was done at

6 months in these patients to determine whether their HVPg response was still maintained. The repeat HVPg could be done in 38/46 patients (83%), as one patient had declined for repeat HVPg, while seven patients had died during the 6-month follow-up. The median interval between the first HVPg and the follow-up HVPg was 6 months (range 5.5–7 months).

The comparison of HVPg results at 6 months with baseline and one-hour post-carvedilol HVPg is shown in Figure 3. At 6 months, the median HVPg had further decreased by a median of 35% to 13.5 mm Hg. According to the response criteria, 35/38 (92%) patients had maintained their hemodynamic response at 6 months. Thus, acute hemodynamic response testing was found to be a reliable method of determining which patients will respond to long-term carvedilol therapy. In only 3/38 (8%) patients the HVPg response was not maintained and their 6-month HVPg value was comparable to their baseline HVPg value.

According to intention-to-treat analysis, assuming the worst-case scenario, those acute-responders who had died during the follow-up (*n* = 7), and those who declined for repeat HVPg (*n* = 1), were considered to have been non-responders in the long-term. Then, the number of patients maintaining their response for long-term was 35/46 (76%).

Taking the most stringent criteria of chronic response: 20% decrease (rather than 10% decrease), and using intention-to-treat analysis, 32/46 (70%) patients were found to be responders at 6 months.

Comparison of Clinical Outcome in Acute-Hemodynamic-Responders and Non-Responders

Patients with acute-hemodynamic-response (*n* = 46) were treated with carvedilol at a dose of 12.5 mg/d (in two divided doses) till the end of the study, in addition to the standard endoscopic therapy. Patients also received standard medical care depending on their clinical status and etiology. All alcoholic patients remained abstinent throughout the period of study. The follow-up period was similar in both the groups. The clinical outcome of patients was assessed under following parameters:

Variceal Bleeding

Patients of acute-hemodynamic-responder group received carvedilol therapy in addition to endoscopic therapy for varices, while patients of acute-hemodynamic-non-responder group received endoscopic therapy alone. During the 6-month follow-up, nine patients developed variceal bleeding. Episodes of variceal bleeding were significantly more common in the acute-hemodynamic-non-responder group than acute-hemodynamic-responder group (6/23 [26%] vs. 3/46 [6%]; *P* = 0.051) (Table 4). Variceal bleeding led to death of one patient in the acute-hemodynamic-non-responder group. Of the three patients who had bleeding in the acute-hemodynamic-responder group, one of them had

Table 2 Hemodynamic Parameters: Baseline and 1 h after Carvedilol (25 mg) in All Patients.

Parameter	All patients (n = 69)			Acute-hemodynamic-responders (n = 46)			Acute-hemodynamic-non-responders (n = 23)		
	Baseline	Post-carvedilol	P value	Baseline	Post-carvedilol	P value	Baseline	Post-carvedilol	P value
HR (beats/min)	87 (61–139)	75 (50–100)	<0.01	87 (61–139)	74 (50–98)	<0.01	86 (62–105)	75 (52–100)	<0.01
MAP (mm Hg)	93 (60–132)	82 (60–125)	<0.01	94 (60–132)	80 (61–113)	<0.01	92 (65–116)	86 (60–125)	0.088
FHVP (mm Hg)	12.5 (5.5–23.0)	13.0 (3.0–24.0)	0.899	12.5 (5.5–23.0)	13.0 (3.0–24.0)	0.203	12.0 (7.0–22.5)	12.5 (3.0–23.5)	0.216
WHVP (mm Hg)	32.0 (23.0–50.5)	29.5 (15.5–46.0)	<0.01	32.2 (23.0–50.5)	28.0 (15.5–46.0)	<0.01	31.0 (25.5–39.0)	30.0 (21.5–40.0)	0.325
HVPG (mm Hg)	19.0 (13.0–30.0)	16.5 (10.0–26.0)	<0.01	20.0 (15.0–30.0)	16.0 (10.0–26.0)	<0.01	18.0 (13.0–24.5)	18.0 (13.0–25.0)	0.823
Percentage reduction in HVPG		13% (–25% to 48%)	–		20% (10%–48%)	–		0% (–25% to 9%)	–
Acute-hemodynamic-responders		46/69 (67%)	–						–
Acute-hemodynamic-non-responders		23/69 (33%)	–						–

Note: All values are in median (range) or n (%).

Table 3 Baseline Characteristics in Acute-Hemodynamic-Responders and Acute-Hemodynamic-Non-Responders.

Parameter	Acute-hemodynamic-responders (n = 46)		Acute-hemodynamic-non-responders (n = 23)		P value (univariate)	P value (multivariate)
Age (years)	50	(26–69)	55	(28–74)	0.670	
Sex					1.000	
Males	43	(94%)	21	(92%)		
Females	3	(6%)	2	(8%)		
Etiology of cirrhosis					0.288	
Alcohol	29	(63%)	12	(52%)		
NASH or cryptogenic	10	(22%)	9	(39%)		
Viral	7	(15%)	2	(9%)		
MELD	13	(6–32)	13	(8–24)	0.932	
CTP score	8	(5–13)	7	(5–12)	0.925	
Child-Pugh class					0.581	
A	9	(20%)	7	(30%)		
B	29	(63%)	12	(52%)		
C	8	(17%)	4	(17%)		
Ascites present	28	(61%)	14	(61%)	1.000	
HE (grade 1–2) present	2	(4%)	1	(4%)	1.000	
History of variceal bleeding	29	(63%)	15	(65%)	1.000	
Transient elastography (kPa) (n = 41)	50.5	(13.9–75.0)	49.0	(15.1–75.0)	0.828	
Esophageal varices					0.794	
Small	19	(41%)	8	(35%)		
Large	27	(59%)	15	(65%)		
Associated gastric varices present	10	(22%)	4	(17%)	0.760	
PHG present	12	(26%)	5	(22%)	0.774	
Hemoglobin (g/dL)	9.5	(6.9–14.5)	9.1	(6.9–17.0)	0.443	
Platelets, $n \times 10^3/\text{mm}^3$	102	(13–417)	100	(26–462)	0.932	
Creatinine (mg/dL)	0.8	(0.4–1.6)	1.0	(0.7–1.6)	0.030	0.015
Sodium (meq/dL)	136	(103–147)	132	(122–141)	0.074	0.521
Potassium (meq/dL)	3.8	(3.2–5.3)	3.9	(3.1–4.8)	0.932	
Bilirubin (mg/dL)	1.6	(0.4–20.9)	1.8	(0.6–7.9)	0.932	
Albumin (g/dL)	2.8	(1.6–4.3)	2.8	(1.9–4.3)	0.798	
INR	1.4	(1.0–3.6)	1.4	(1.2–3.1)	0.443	
Baseline HVPG (mm Hg)	20.0	(15.0–30.0)	18.0	(13.0–24.5)	0.074	0.010

Table 4 Comparison of Clinical Outcome in Acute-Hemodynamic-Responders and Non-Responders.

Outcome	Acute-hemodynamic-responders (n = 46)		Acute-hemodynamic-non-responders (n = 23)		P value
Variceal bleeding	3	(6%)	6	(26%)	0.051
Worsening ascites	12	(26%)	17	(74%)	<0.01
Hepatic encephalopathy	9	(20%)	8	(35%)	0.236
Change in MELD points	−1.5	(−6.0 to +7.0)	+1.8	(−1.6 to +12.8)	0.001
Change in CTP score	−1	(−3 to +2)	+1	(−2 to +3)	<0.01
Died	7	(15%)	3	(13%)	1.000

Note: Of the six patients who had bleeding in the acute-hemodynamic-non-responder group, three were on primary prophylaxis and three were on secondary prophylaxis.

Figure 2 Subgroup analysis data for variceal bleeding, stratified according to primary and secondary prophylaxis. (Note: There was no statistically significant difference between the four outcome groups, mainly due to small number of patients in each group.)

not maintained his HVPg response at 6 months. Of the six patients who had bleeding in the acute-hemodynamic-non-responder group, three were on primary prophylaxis and three were on secondary prophylaxis. The subgroup analysis data for variceal bleeding, stratified according to primary and secondary prophylaxis, is shown in Figure 2.

Ascites

At baseline, 42 (61%) patients had ascites (mild in 40 and moderate-to-tense in 2) while 27 (39%) had no ascites. Of 27 patients who had no ascites at baseline, during follow-up, 12 of them developed new ascites. Of 42 patients who

had ascites at baseline, it improved with diuretics in 19 patients, remained static in 4 patients, and further increased in 19 patients. For the purpose of our study, 'worsening of ascites status' was defined as either development of new ascites, or increase in pre-existing ascites in the form of higher diuretic requirements or frequent requirement of paracentesis. So out of 69 included patients, the ascites status had worsened in 29 (42%) patients. The worsening of ascites was significantly more common in the acute-hemodynamic-non-responder group than in acute-hemodynamic-responder group (17/23 [74%] vs. 12/46 [26%]; $P < 0.01$) (Table 4).

Hepatic Encephalopathy

Patients with grade 3–4 hepatic encephalopathy were excluded at the time of enrollment in the study. Of the included patients, only 3 had grade 1–2 hepatic encephalopathy. During follow-up, 17 patients developed episodes of hepatic encephalopathy and of them, in 10 patients, hepatic encephalopathy was one of the terminal events. There was no statistically significant difference in number of patients developing hepatic encephalopathy in the two groups (Table 4).

Mortality

A total of 10 patients died during the follow-up. Reason for death included worsening liver function leading to multi-organ failure ($n = 8$), variceal bleeding ($n = 1$), and severe ongoing alcoholic hepatitis despite abstinence ($n = 1$). The mortality rate was similar in acute-hemodynamic-responder and acute-hemodynamic-non-responder groups (7/46 [15%] vs. 3/23 [13%]; $P = 1.0$) (Table 4).

Figure 3 Median HVPg in patients who were acute-hemodynamic-responders ($n = 46$) and in whom HVPg was repeated at 6 months ($n = 38$). The HVPg response was maintained at 6 months in most patients. Legend: * $P < 0.01$ compared to baseline; ** $P < 0.01$ compared to baseline.

CTP and MELD Scores

Of the patients who survived and completed the 6-month follow-up, the MELD and CTP scores were assessed at the end of 6-month follow-up period. The MELD decreased by a median of 1.5 points in the acute-hemodynamic-responder group while it increased by a median of 1.8 points in the acute-hemodynamic-non-responder group. This difference was statistically significant. Similarly, the CTP score decreased by median 1 point in the acute-hemodynamic-responder group while it increased by median 1 point in the acute-hemodynamic-non-responder group. This difference was also statistically significant (Table 4).

Adverse Effects to Carvedilol

Carvedilol at the dose of 12.5 mg/d (in two divided doses) was very well tolerated. There were no significant adverse effects and no patient required dose reduction or stoppage of drug due to adverse effects.

DISCUSSION

To summarize the results, our study showed that before beginning carvedilol therapy, acute hemodynamic response testing is a reliable method of predicting which patients are more likely to respond to carvedilol in long-term. In our study, the acute-hemodynamic-response was seen in 67% of patients and most (92%) of these acute responders maintained their response to carvedilol over long-term (6 months). In addition, carvedilol therapy led to better clinical outcome in these patients compared to non-carvedilol treated patients who were not acute responders. Acute responders had lesser episodes of variceal bleeding, better ascites control, and improved MELD and CTP scores on carvedilol, than non-carvedilol treated non-responders. However, survival remained similar in both the groups. Thus, acute hemodynamic response testing, followed by carvedilol therapy to responders, leads to improved clinical outcome.

NSBBs are very useful drugs in preventing first variceal bleeding and re-bleeding in patients with cirrhosis. These drugs reduce portal pressure by two mechanisms: (a) by blocking beta-1 receptors and reducing cardiac output and (b) by blocking beta-2 receptors, producing splanchnic vasoconstriction and reducing portal flow.¹⁴ Longitudinal studies in patients treated with NSBB both in primary and secondary prophylaxis have suggested a very low residual risk of bleeding if there is a decrease of HVPg by at least 20% of baseline or to values ≤ 12 mm Hg. Patients achieving such a target reduction in portal pressure have been defined hemodynamic responders.³ Propranolol has been the most commonly used NSBB. Carvedilol is a new NSBB with an additional property of vasodilatation due to its intrinsic anti- α_1 adrenergic activity and its capacity to

enhance the release of nitric oxide.^{2,3} It reduces portal pressure not only by decreasing portal-collateral blood flow (as all other NSBB) but also by diminishing the functional component of hepatic vascular resistance which is increased in cirrhosis.³ Thus, carvedilol is a more potent agent than propranolol in reducing portal pressure and might be effective in more patients. In a recent meta-analysis by Aguilar-Olivos et al. on hemodynamic effect of carvedilol versus propranolol in cirrhotic patients, 4 trials involving 153 patients were analyzed.¹⁵ It was found that HVPg decreased more with carvedilol than with propranolol, and carvedilol was superior to propranolol for reducing HVPg by $\geq 20\%$ from the baseline value or to ≤ 12 mm Hg. Overall adverse events did not differ between. The authors concluded that there is evidence suggesting that carvedilol is more effective than propranolol for improving the hemodynamic response.¹⁵ In another meta-analysis by Sinagra et al.,¹⁶ involving 5 studies (175 patients), the summary mean weighted difference in % of reduction in HVPg was: acute -7.70 (CI $-12.40, -3.00$), long-term -6.81 (CI $-11.35, -2.26$), overall -7.24 (CI $-10.50, -3.97$), favoring carvedilol. The authors concluded that carvedilol reduces portal hypertension significantly more than propranolol.¹⁶ Thus, now carvedilol is gradually becoming the preferred drug for use in portal hypertension.

NSBBs are not effective in all cirrhotic patients, and satisfactory reduction in portal pressure is possible in only a third to half of patients with propranolol and nadolol¹⁷ and in 60% of patients with carvedilol.¹⁵ The gold standard method to know whether a patient is a hemodynamic responder to NSBB is to measure the HVPg at baseline, and then repeat HVPg measurement after chronic administration of NSBB. However, concerns have been raised in relation to the feasibility, the clinical appropriateness, the risks and the costs of repeated HVPg measurement.^{4,3} Also, a substantial number of patients re-bleed before their hemodynamic response can be assessed. This problem could only be partially solved by re-measuring the HVPg after a shorter interval (even less than 1 month).^{3,18} To do away with problems of repeated HVPg measurements, acute hemodynamic response testing seems to be the answer. Many studies have investigated the role of acute HVPg response to intravenous or oral propranolol in predicting the risk of bleeding and survival.⁵⁻⁹ This was suggested to be a more cost-effective strategy than the chronic evaluation of HVPg response and might be useful to guide therapeutic decisions in these patients. Studies have suggested that for acute response testing, even a lower threshold (HVPg reduction of 10–12%) might be adequate for bleeding risk discrimination.^{3,9,19}

As against propranolol, carvedilol has been used in relatively fewer studies for acute hemodynamic response testing.^{13,20-25} Moreover, most of these studies have used small number of patients (maximum 18) for response

Table 5 Percentage Reduction in HVPG at 60–90 min after 12.5–25 mg of Carvedilol in Various Studies.

Study	N	Mean percent decrease in HVPG in all patients
Silkauskaitė et al. ²⁰	10	29.6
Lin et al. ²¹	11	18.6
De et al. ¹³	18	27.7
Tripathi et al. ²²	10	23.9
Stanley et al. ²³	17	20.8
Sekiyama et al. ²⁴	10	15.0
Forrest et al. ²⁵	16	18.5
Present study	69	14.5
Mean	161	18.9

Note: In our study, the median percent reduction in HVPG was 13% while mean percent reduction was 14.5%.

testing (Table 5) and none of these studies have followed responders for long-term. In this direction, ours is the only study which has not only used acute hemodynamic response testing for a large number of patients ($n = 69$), but also followed acute responders for long-term, and repeated HVPG at 6 months to see in how many the carvedilol response was still maintained. The most important finding of our study has been that most patients who have acute response to carvedilol, maintain their response over long period. Hence, based on the results of our study, we can conclude that a single time HVPG measurement with acute response testing is simple, reliable, and cost-effective method for identifying responders. This finding extends the findings of other studies which have shown that the HVPG response after acute administration of carvedilol correlates with the response rates to the drug for up to 2 weeks.^{13,20} The response may be generalized for all NSBBs, and not specific for individual drugs as shown by Villanueva et al. who showed that acute HVPG response to propranolol correlated with chronic HVPG response to nadolol,⁹ and Hobolth who showed that acute response to propranolol can predict the long-term HVPG response to carvedilol.²⁶ Acutely, carvedilol causes a modest reduction in HVPG ranging from 14.5% (our study) to about 30% (Silkauskaitė et al.²⁰). On chronic administration of carvedilol, the response is more marked, and in our study HVPG reduced by 35% at 6 months.

We also showed that carvedilol treated patients had a better clinical outcome than non-carvedilol treated patients. Beyond portal pressure reduction, carvedilol and other NSBB may also have a pleiotropic protective effect, as shown by many other studies.^{27,28} In a recent multi-center study by Stanley et al., comparing EVL therapy with carvedilol, the latter was not found to be superior to VBL in the prevention of variceal rebleeding.²⁷ This was expected, as the current recommendation for secondary prophylaxis according to Baveno V consensus²⁹ is

combination of beta-blockers and band ligation, as it results in lower re-bleeding compared to either therapy alone. However, an interesting finding of the study was that the overall mortality in the carvedilol group was lower than the VBL group (27% vs. 52%), although this did not reach statistical significance. Most deaths in the carvedilol group were bleeding related, whereas in the VBL group the vast majority was due to non-bleeding causes, which could suggest a pleiotropic protective effect of carvedilol in cirrhotic patients. The survival for Child-Pugh class B patients was significantly higher for patients given carvedilol compared with VBL, while there was no mortality difference for Child-Pugh class A or C patients, suggesting Child-Pugh class B patients benefit most from carvedilol.²⁷ Our study also had majority of Child-Pugh class B patients (59%), which might have contributed to better clinical outcome in carvedilol responders. Recently, “window hypothesis” has been suggested describing the survival benefit of beta-blockers for cirrhotic patients in the mid (early decompensated) phase of the disease, but not for those with either well compensated or end-stage cirrhosis.^{30,31} Outside of this window, beta-blockers may be ineffective in early cirrhosis with some increase in adverse events, and potentially harmful in advanced cirrhosis.³¹

There has been concerns raised that carvedilol may have a greater potential to cause systemic hypotension, especially in patients with cirrhosis and ascites. In a study by Bañares et al., carvedilol caused significant arterial hypotension with average decrease in mean arterial pressure of -17.2% in the carvedilol group versus -3.4% in the propranolol group.³² In a follow-up study, 51 patients were randomized to long-term carvedilol or propranolol.³³ This study again showed a significant decrease in mean arterial pressure of -11% in the carvedilol group vs. -5% in the propranolol group. Patients receiving carvedilol also had significant increases in plasma volume, body weight, and worsening of pre-existing ascites. However, in our study, carvedilol was very well tolerated by all the patients. Acutely, carvedilol caused a decrease in mean arterial pressure from 93 to 82 mm Hg (12% decrease) but in no patients the mean arterial pressure dropped below 60 mm Hg. With chronic administration in the dose of 12.5 mg/d, carvedilol was well tolerated with no patients requiring stoppage or dose reduction. In fact, carvedilol treated patients had better ascites control than non-carvedilol treated patients.

The highlights of our study are that we have included a good number of patients ($N = 69$), which are well studied and followed; we have performed $69 + 38 = 107$ HVPGs, and the 6-month follow-up is complete in almost the whole cohort. Although there are previous studies showing that the acute response to carvedilol is a good predictor of long-term response, our study is the largest reported so far and the delay between the acute and chronic HVPG is also the longest.

But our study had also a few limitations: First, acute non-responders received only EVL whereas responders received a combination of carvedilol and EVL. So non-responders were at a disadvantage in the sense that they only received EVL whereas acute responders received a combination therapy. So the conclusion that acute responders had lower bleeding rates compared to acute-non-responders should be interpreted with caution because acute non-responders received only single therapy while responders received dual therapy. Second, this study was open labeled, non-placebo, uncontrolled trial. Hence, the better clinical response with carvedilol should also be interpreted with caution, since the groups used to draw this conclusion may not be strictly comparable. The study could have been better designed had we offered placebo treatment to carvedilol non-responders, thus making it single blinded, rather than open labeled. Other alternative study design could have been continuing carvedilol even in acute non-responders, and repeating HVPG at 6 months, to see how many of acute non-responders actually turn out to be long-term responder. The other limitation could be that in the study, we clubbed the patients of primary prophylaxis and secondary prophylaxis in one group. The responders received dual therapy (carvedilol plus endoscopic therapy), while the non-responders quit carvedilol and received endoscopic therapy alone. Thus, while responders were adequately treated (or, for the case of primary prophylaxis, probably over-treated), the therapy used for non-responders is probably insufficient (at least in previous bleeders). However, this would not have impacted our results, as there was no difference in proportion of primary and secondary prophylaxis patients in responders versus non-responders (Table 3). Besides, of the six patients who had bleeding in the acute-hemodynamic-non-responder group, three were on primary prophylaxis and three were on secondary prophylaxis.

In conclusion, acute hemodynamic response testing is an easy, safe, and reliable method of determining which patients are likely to respond in long-term to carvedilol therapy. Acutely, carvedilol response is seen in up to 67% of patients and most (92%) of these acute responders maintained their response to carvedilol over long-term (6 months). Carvedilol therapy in these acute responders leads to better clinical outcome in terms of lesser episodes of portal hypertensive bleeding, better ascites control, and improved cirrhosis severity scores. Thus, we propose that carvedilol could now replace propranolol as the beta-blocker of choice in portal hypertension, and the therapy should be guided by one time HVPG at baseline with response testing. Which drug should be offered to carvedilol non-responders is still not clear; hence, further research should be focused on management of carvedilol non-responders.

AUTHORS' CONTRIBUTION

Study design, supervision – AA, AK, PS.

Patient enrollment, data collection – VK, VG, MG, RC.

Data analysis, statistics – AK.

Drafting of manuscript – VK, AK.

Critical revision for important intellectual content – PS, VS, NB.

CONFLICTS OF INTEREST

The authors have none to declare.

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