Original Research Article

"Acute versus chronic hemodynamic response of Carvedilol in Chronic Liver Disease with Portal hypertension"

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Abstract

Background: Hemodynamic studies give objective method to measure the response but need to be repeated during the course of therapy. Data comparing acute with chronic hemodynamic response of Carvedilol is scarce and needs to be studied further to elucidate the course and predictors of response, so the single hemodynamic study envisages the long-term response. **Aims and Objectives:** The purpose of this study was 1.To assess and compare the acute and chronic hemodynamic response to Carvedilol along with their predictors in Cirrhotic patients.2.To evaluate if acute response is maintained long term. **Methods**: In one hundred two consecutive patients of chronic liver disease with esophageal varices, Hepatic Venous Pressure Gradient (HVPG) was measured at baseline and 90 minutes after initial administration of 12.5 mg of Carvedilol to assess the acute response. These patients were reassessed at 3 months of dose optimization for chronic response. The acute responders were compared with chronic responders. **Results:** Acute response was seen in 51% and chronic in 62% patients. Most of the patients who responded to optimized therapy after no acute response belonged to CTP A. Mean reduction of HVPG in responders was 4.5± 2.2 mmHg to loading dose and 5. 5± 1.7 mmHg at 3 months. Low Cardiac output (CO), more than 2.5 mmHg drop acutely and dose optimization were independent predictors of response for acute, chronic and chronic response with no acute response respectively. **Conclusion**: Acute response assessed by hemodynamic study at initiation of treatment is important predictor of chronic response and is maintained over period of time. Dose optimization to achieve response is more appropriate for CTP A then B and C.

Keywords: Hemodynamic study, Carvedilol, acute response, chronic response, Cardiac output (CO).

Introduction

Variceal bleed is one of the major and fatal complications of portal hypertension.[1] Although Endoscopic Variceal Ligation (EVL) is the preferred first-line modality for secondary prevention after a first variceal bleed, Beta-Adrenergic Receptor Blockers (BB) are equally effective for primary prevention and have now evolved into a frontline strategy for the prevention of variceal bleeds.[1-3] Over time, BBs have gained repute not only for decreasing the risk of variceal bleed by reducing portal pressure but also increased survival by lowering long-term risk of developing other complications like Hepatorenal Syndrome, ascites, Spontaneous Bacterial Peritonitis, and Hepatocellular Carcinoma, giving them an edge over EVL.[1,4,5] Nevertheless, only half of the patients showed hemodynamic response to traditional NSBBs like propranolol or nadolol.[6,7] Carvedilol is a newer, potent BB with combined Alpha and Beta blocking properties that have replaced traditional NSBB owing to its better hemodynamic outcomes, efficacy, and side effect profile. In addition, Carvedilol has shown survival benefit independent of reducing bleeding complications, likely by decreasing gut congestion and reducing microbial translocation thereby decreasing the chances of SBP and infections. [8,9]Hepatic Venous Pressure Gradient (HVPG) has a direct correlation with complications of Portal Hypertension with a high probability of variceal bleeding associated at HVPG above 12 mmHg. [7,10] The benchmark to know if a patient will be a responder to BB is the degree of decrease in HVPG from baseline during acute testing, and then maintain this response long term , demonstrated by repeated hemodynamic study . Several hemodynamic studies evaluated acute response [7,11,12] and chronic response [11,12,13,14,15] after BB administration. However, most of them have not compared acute and chronic response rates considering CTP Class.[16] This is important as pathophysiology, hemodynamics, and tolerance to drugs varies during course of liver disease. Moreover, the factors responsible for lack of response have also not been studied in past, which could help us to determine a subset of patients who may need other modalities of treatment from the outset. Additionally, there concerns regarding the feasibility, clinical appropriateness, risks, and costs of repeated HVPG measurement. In light of this we contemplated the present study 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 a better clinical outcome. We also assessed the factors associated with increasing the response rates with dose optimization in patients who initially showed a lack of response during acute testing.

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Material and Methods

This study was a prospective study conducted in the Department Gastroenterology of SKIMS, Tertiary Care Centre of North India. Written informed consent was taken from all participants and the Institutional Ethics Committee cleared the study protocol. All consecutive patients of cirrhosis who consented for hemodynamic assessment from 2010 to 2013 were included in the study.

Inclusion Criteria

Adults with

- Esophageal Varices on Endoscopic gastroduodenoscopy(EGD)
- No past history of Malena or Hematemesis
- Baseline HVPG of more than 12mmHg

Exclusion Criteria

- Age <18 years
- Non cirrhotic portal hypertension
- Known malignancies/ HCC
- Acute or chronic kidney disease with creatinine more than >1.5mg/dl
- Active IV drug or Alcohol Abuser
- Liver Failure (INR more than 2.5 and bilirubin more than 5mg/dl)
- Severe systemic illness or sepsis
- Chronic pulmonary disease
- Psychiatric illness or lack of capacity to give informed consent
- Pregnant or lactating females
- Contraindications / allergies to Carvedilol use
- Patients already on any of portal hypertension lowering drugs, carvedilol or other BB or nitrate etc.

Cirrhosis was diagnosed on clinical, biochemical, radiological parameters and liver biopsy if so required. Ascites was defined on the basis of International ascites club 2003 as Grade I if picked up only on USG, grade II if moderately symmetrical distension or grade III if grossly distended abdomen with ascites. Esophageal varices were defined by Baveno consensus as large or small if more or less than 5mm respectively.

HVPG Measurement

- Under the fluoroscopic guidance hepatic vein catheterization was performed according to the standards outlined by Bosch *et al.*
- Wedged hepatic venous pressure (WHP) was measured with help of 7F balloon tipped catheter advanced into right main hepatic vein.
- HVPG was determined by the difference of wedged and free hepatic pressures (WHVP – FHVP)
- Cardiopulmonary pressures, such as pulmonary artery pressure (PAP), wedged pulmonary pressure (WPP), and right atrial pressure (RAP) were measured with a Swan-Ganz catheter, advanced to the pulmonary artery.
- An automatic sphygmomanometer was used for noninvasive MAP measurement.
- Continuous ECG monitoring was used to calculate heart rate (HR).
- Systemic vascular resistance (SVR) was calculated from formula
- SVR = MAP – RAP/CO × 80.

Statistical analysis: Statistical analysis was performed using a statistical software program SPSS version 20 (IBM). Continuous variables were expressed as mean and standard deviation (Mean (SD)and Range. Quantitative data between two groups was compared with the use of Student *t*-test for parametric data and Mann-Whitney U test for non-parametric data and Kruskal Wallis Test. Pearson chi-square test and Fisher's exact test were used for categorical data to see the association of variables. Odds ratio were used at appropriate places to see the strength of associations. All p values were two-tailed; p value of < 0.05 was considered statistically significant. Chronic response was determined by analyzing univariate and multivariate logistic regression.

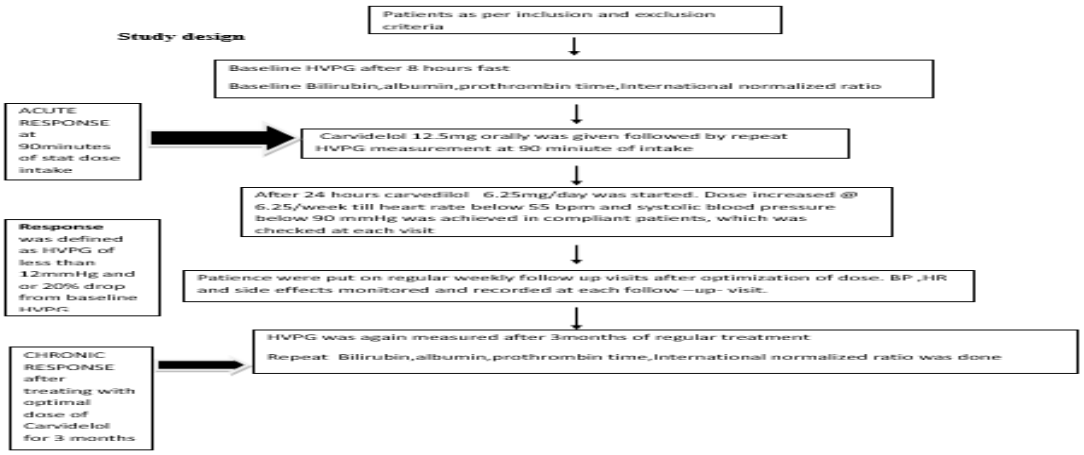

Fig 1: Study design

Results

One hundred and two patients of Chronic liver disease of different etiologies with esophageal varices and baseline HVPG of more than 12mmHg were enrolled, after excluding 98 patients as per exclusion criteria. Demographic features and baseline parameters are summarized in the table 1.

Table 1: Demographic features and Baseline parameters

Parameters	Description
Age in years Mean (SD)	58.35(6.62)
Males/ Females	63 (61.76%) /39 (38.23%)
Child Class (A: B:C)	43:32:27
Etiology (Alcohol: Viral: NASH or Cryptogenic: AIH)	31:37:29: 5
Esophageal varices (small: large)	34(33.3%):68(66.6%)
Ascites (Grade I: II: III)	6:25:8
Serum Albumin(mg/dl)	3.20±0.49

Total Bilirubin(mg/dl)	1.96±0.81
Prothrombin	14.13±1.91
INR	1.29±0.16

Fifty-two patients (51%) achieved hemodynamic response after a fixed loading dose of 12.5mg carvedilol was given to 102 patients and figures increased to 62(60.8%) after three months of optimized therapy, thereby implying that 10 (9.8%) of patients responded to increased dose as shown in Figure 1.Figure 2 demonstrates acute and chronic response in different child classes. Eight out of 10 patients responding to optimized treatment after 3 months were amongst CTP-A. Response according to CTP class are given in table 2. Acute responders maintain their hemodynamic response. Acute non responders are less likely to respond with continued therapy if patient had higher CTP score.

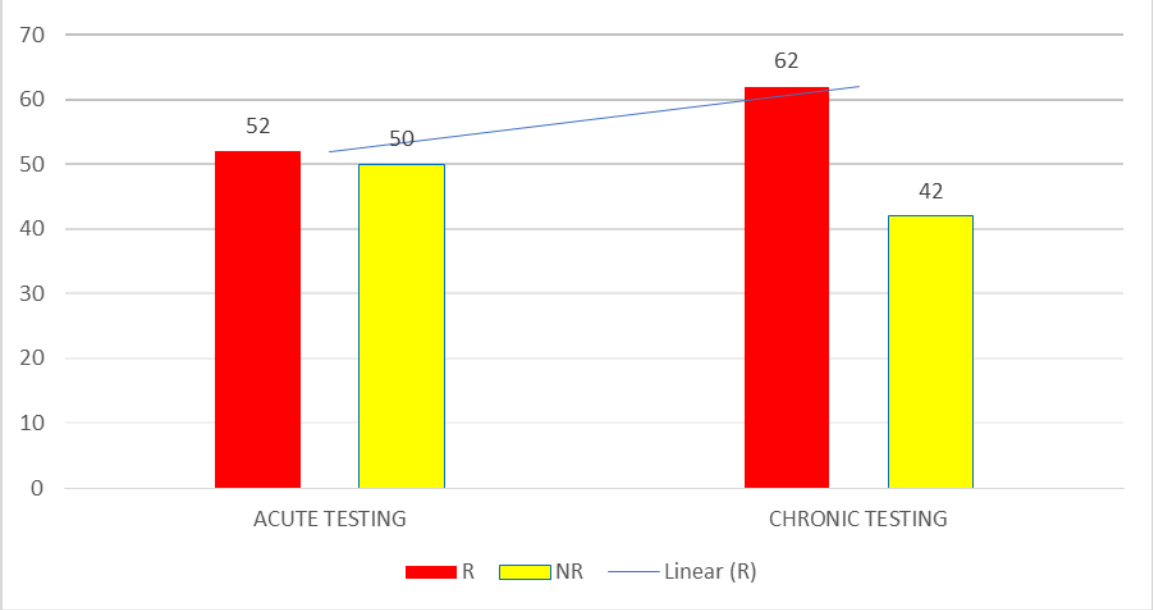

Fig. 1: Hemodynamic response to Carvedilol

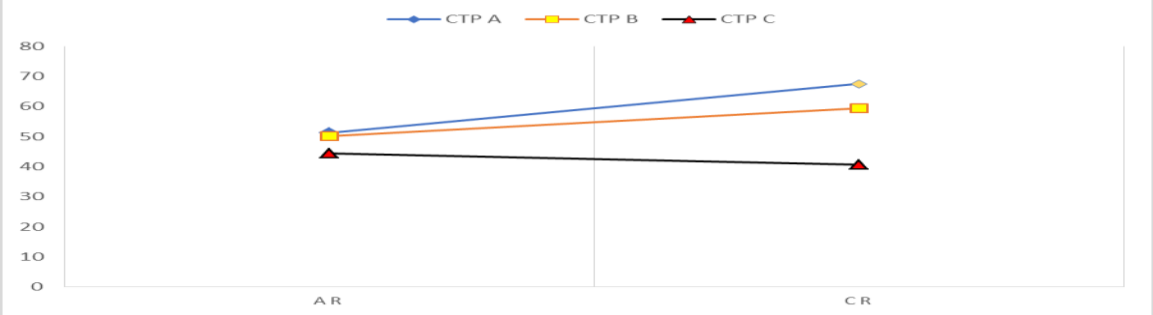

Fig. 2: Response as per CTP Class

Table 2: Response as per CTP Class

CTP class	Acute Response	Chronic Response
A	22/43(51.2%)	29/43(67.44%)
B	16/32(50%)	19/32(59.37%)
C	12/27(44.4%)	11/27(40.7%)

Mean baseline HVPG of 16.75± 2.12 mmHg decreased to13.07± 2.32 mmHg after 90 min of carvedilol ingestion and later to 12.60mmHg after three months of treatment. Mean fall in HVPG in responders was 4.5± 2.2 mmHg compared to 2.4 ± 01.9 mmHg in non-responders and figures at 3 months were 5. 5± 1.7 mmHg and 2.8 ± 1.6 mmHg in responders and non-responders respectively.

Low baseline CO was found to be significantly associated to acute response on univariate as well multivariate analysis while high MAP was significant predictor of acute response only on univariate analysis. Low baseline CO predicted chronic response on Univariate analysis but not on multivariate analysis. More than 2.5 mmHg fall in HVPG during acute response predicted chronic response on Univariate analysis and was found as independent predictors of chronic response on multivariate analysis ($p<0.05$). Escalating the dose above 18.5mg and lesser decline in HR was found to be the predictors of chronic response with no acute response.

No other demographic, biochemical or hemodynamic factor was found statistically significant between responders and non-responders. Even though not statistically significant, mean dose of carvedilol was higher among non-responders (19.2 ±5.7 mg) as compared to responders 18.7± 5.1mg).

Two of our patients were excluded as they developed hypotension meriting discontinuation of therapy. Nine patients had minor side effects, seven of them being non responders, which resolved within few days without need of drug discontinuation.

Table 3: Hemodynamic parameters at Baseline, 90 minutes after Acute Administration of Carvedilol and at 3 months after dose optimization

Parameter	Pre treatment Mean (SD)	Acute Post treatment Mean (SD)	Chronic Post treatment Mean (SD)	P value
CO (liter/min)	7.525 (0.19)	6.502 (0.23)	6.38 (0.15)	<0.001
HR (beats/min)	79.45 (2.50)	61.46 (2.13)	57.45(2 .44)	<0.001
MAP (units)	89.53 (2.42)	78.02 (1.86)	75.54 (1.97)	<0.001
FHVP (mmHg)	8.28 (1.85)	9.45 (1.91)	9.45 (1.90)	<0.001
WHPG (mmHg)	25.08 (2.55)	22.78 (2.58)	22.04 (2.56)	<0.001
HVPG (mmHg)	16.75 (2.12)	13.07 (2.32)	12.60 (2.24)	<0.001

CO: Cardiac Output; HR: Heart Rate; MAP: Mean Arterial Pressure; FHVP: Free Hepatic Venous Pressure; WHPG: Wedged Hepatic Venous Pressure; HVPG: Hepatic Venous Pressure Gradient

Discussion

BB therapy has become a cornerstone in the management of Portal Hypertension as it not only helps in reducing the chances of variceal bleed but also has other systemic benefits giving it a relative advantage over EVL.[1] Combined EVL and BB treatment as secondary prophylaxis is thus recommended according to Baveno VI consensus and is superior to either modality alone.[17]

Many patients on empirical BB therapy present with variceal bleed as they are never assessed for hemodynamic response in the clinical setting. For a better understanding of the hemodynamic response and factors associated thereof, several Hemodynamic studies have been conducted, including a few by our group. [8,9,18,19] Owing to cost factors and logistics, it's not practicable to do these studies in every single patient, as well as repeat the measurements during the treatment. Hence there is a necessity of studying the factors predictive of Acute and Chronic Response to BBs, and whether the acute response is maintained in the long term, thus avoiding the need for repetitive hemodynamic studies.

In hemodynamic studies done till now, there is enough evidence to prove that carvedilol has better acute and chronic response than NSBB. Banares R *et al* [20] were amongst the first few groups to show carvedilol to be a more potent anti-portal hypertensive drug than propranolol owing to its additional intrinsic anti-alpha 1-adrenergic activity. Forrest *et al* [12] were the first to demonstrate acute hemodynamic changes after oral carvedilol in cirrhotic patients to the extent of 81%, which is much higher than 51% in our study. A likely explanation for this difference is the use of a higher dose of Carvedilol (double than ours) as well as the lower cut off of defining the response (decrease in HVPG of 10% compared to 20% in our study). Lin HC et al [7] demonstrated that the acute administration of carvedilol is more effective than propranolol plus isosorbide-5-mononitrate in combination, with a greater decrease in HVPG and increased Hepatic blood flow. Reiberger T et al [6] showed that carvedilol is effective even in propranolol non-responders with a response up to 56% and a greater drop in HVPG. Most importantly they showed Carvedilol improves overall survival and patients had a lesser rate of decompensation as well.

Numerous hemodynamic studies have been conducted to study acute[7,11,12] and chronic [11,13,14,15]effects of carvedilol either separately or sequentially[6,] and the outcomes showed considerable variations. These differences may be due to heterogeneous study populations in terms of etiology and CTP Classes. Different doses of Carvedilol, more [12], same [11,14,15] or less [13,21] than our study was used and response defined either more than 10% or 20% drop in portal pressure. In addition, even selection criteria have been different. Some have studied carvedilol response separately or compared it with propranolol or combination therapies. Understandably overall acute response varied from 40 to 70 % and chronic response varied from 60% to 80%. If all confounding factors are kept in consideration our results correspond well with the past literature [6,10,15]

All acute responders maintained their response chronically and 10 (9.8%) patients who initially had no Acute Response, showed Chronic Response after dose optimization at 3 months, 8/10 of these were Child class A. Implying that for CTP B and C, Acute non-responders are unlikely to respond after dose optimization whereas this strategy is more applicable for CTP A, possibly because they tolerated an increase in dose better. Interestingly, the overall chronic response slightly decreased in CTP C as against the acute response, inferring that larger dose are not tolerated leading to more side effects. It may suggest that optimization of the dose doesn't help CTP C and may even cause harm as shown in past studies [22]. Carvedilol even if continued in them owing to their other beneficial systemic effects [1] should be in low dose in combination with EVL upfront. Moreover , none of the acute responders lost their response over a long period signifying that a single hemodynamic study done at the beginning of treatment is enough, corresponding to some previous observation [14,15,24]. Villanueva C *et al* observed in their study correlation between acute and chronic changes in HVPG ($r = 0.62$; $P = .01$) [24]. They also showed that chronic responders had a lower probability of bleeding than non-responders ($P < .001$). Hobolth L *et al* also found when using ROC curve analysis, an acute decline in HVPG of ≥12% was the best cut-off value to predict long-term HVPG response to propranolol [25]. Silkauskait E et al [14] also corroborated that acute response correlates with chronic response.Knowing that cardiovascular tolerance for Carvedilol develops steadily, our approach of escalating dose slowly according to clinical parameters is physiologically more appropriate. Previous studies where larger doses were used at the outset, observed more side effects and needed withdrawal of treatment.[11] Low cardiac output proved a statistically significant predictor of acute as well chronic response in univariate analysis. However, on multivariate analysis it proved to be an independent predictor only for the acute response but not for chronic response ($p < 0.05$). We presumed that as carvedilol improves Cardiac Performance,so over a period it might lead to better Cardiac Output and decrease systemic venous congestion reducing portal pressures. Nevertheless, it is only a hypothesis and needs further elucidation.

MAP was found to be a predictor of acute response but not for the chronic response on univariate analysis, though on multivariate analyses it wasn't statistically significant. Liach et al in their work showed MAP to be an independent predictor of survival.[23]The absence of ascites and adverse events was also predictive of Chronic Response on Univariate analysis but didn't appear to be significant on multivariate analysis. More than 2.5 mmHg fall in HVPG was found to be an independent predictor of Chronic Response on univariate as well as Multivariate analysis ($p < 0.05$). This again reiterates the fact

that acute response predicts chronic response and has been demonstrated in previous studies as well. [25,26] Two of our patients required discontinuation of treatment due to hypotension, both of them were CTP C and were excluded from the study. Nine of our patients reported minor side effects that did not warrant discontinuation. The advantage of our study is that our study had relatively larger study population than all previous hemodynamic studies on carvedilol. We started from a lower dose and increased it slowly which led to lesser dropout, more tolerance, and additional response in around one-tenth of patients. We continued carvedilol even in non-responders which led to better survival in both groups.

Conclusion

To conclude our study confirmed that acute response can envisage chronic response and is maintained throughout treatment. Thus, it may suffice to plan treatment protocol after the acute hemodynamic study only and avoid repeated hemodynamic studies. Gradual dose escalation increased tolerance and decreased the dropout rates leading to the chronic response in patients even without initial response in around a tenth of patients. Most of these patients were from CTP Class A, implying that in Acute non-responders in CTP B and C a second-line treatment for varices is preferred, although patients can be continued on a small tolerable dose of BB owing to systemic beneficial effect. Non-responders and responders did not significantly differ in survival rates.

Recommendation

To get a better insight regarding factors influencing response, larger studies with more homogenous patient population in terms of CTP class and etiology needs to be contemplated. Moreover, predictors of hemodynamic response need further elucidation, and it's important that we evaluate more clinical parameters so that decisions regarding the addition of interventional therapy or alternative pharmacological management can be taken early in clinical scenarios and even without hemodynamic studies.

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