# Effect of Carvedilol on Portal Pressure Estimated By Hepatic Vein Doppler Ultrasound Waveform and Damping Index in Cirrhotic Patients

Qurban Hussain<sup>1</sup>, Aly Haider Badruddin<sup>1</sup>, M. Azhar Chaudhry<sup>1</sup>, Fayyaz Ahmad<sup>2</sup> and Amanullah Abbasi<sup>3</sup>

# ABSTRACT

**Objective**: To assess the effect of Carvedilol in reducing portal pressure estimated non-invasively by studying Doppler ultrasound waveforms (DUS) and hepatic vein Damping Index (DI).

Study Design: Quasi-experimental study.

**Place and Duration of Study**: Department of Medical ICU in collaboration with Department of Radiology, JPMC, over a period of 6 months (June 1st to 30th November, 2008).

**Methodology:** Of the enrolled 65 patients, 47 patients (33 males and 14 females) completed the study. The mean age was 47.4 years. Cirrhotic patients of Hepatitis B, C, D (delta), B and C combined, B and D combined with varying degrees of portal hypertension were included in the study. Cirrhotic patients with bronchial asthma, congestive heart failure, Insulin dependent Diabetes, portal vein thrombosis and hepatorenal syndrome were excluded from the study. The patients were examined by color flow Doppler of the right hepatic vein before and after administration of Carvedilol. Their waveforms and Damping Index (DI) were recorded and compared by Wilcoxon signed ranks test through SPSS version 12.0. Responders were described as those showing a positive change in wave forms or a decrease of 0.10 or more in DI.

**Results:** Of the 47 patients, 30 (63%) showed a positive response and 10 (21%) showed no favorable response to Carvedilol, while 7 (14%) patients showed deterioration. The mean DI on DUS dropped from 0.62 to 0.41 in responders after treatment, while in the non-responders it ranged between 0.42 and 0.57.

**Conclusion**: Ultrasonography Carvedilol reduced portal pressure of cirrhotic patients, as measured indirectly by the damping index of hepatic waveform by Doppler.

Key words: Portal pressure. Doppler ultrasound. Hepatic vein Doppler. Damping index. Carvedilol.

## INTRODUCTION

Portal hypertension is a common sequel of chronic liver disease and portal pressure elevations closely parallel development of complications, like variceal bleeding. Hence, portal pressure measurements are vital not only to pre-empt these serious outcomes but also to study the effect of any pressure lowering treatment that is instituted.<sup>1,2</sup>

The gold standard method of determining portal pressure involves accessing the hepatic vein through a femoral catheter and measuring the wedged and free pressures. The difference of these two pressures is called the hepatic vein pressure gradient (HVPG), which is closely related to the development of complications of portal hypertension. The elevation of HVPG from a normal of 1-3 mmHg to > 12 is associated with development of

<sup>1</sup> Medical ICU, Jinnah Postgraduate Medical Centre, Karachi.

<sup>2</sup> Department of Radiology, Jinnah Postgraduate Medical Centre, Karachi

<sup>3</sup> Ward 7, Jinnah Postgraduate Medical Centre, Karachi.

Correspondence: Dr. Qurban Hussain, Flat 4B III, Doctors Colony, Jinnah Postgraduate Medical Centre, Karachi. E-mail: drqurbanhussain@hotmail.com

Received September 16, 2009; accepted July 13, 2010.

ascites and greater chances of variceal rupture.<sup>1</sup> Severe portal hypertension (PH) is usually defined as an HVPG  $> 15 \text{ mmHg.}^3$ 

Conventionally, the non-selective  $\alpha$ -/ $\beta$ -blocker, propranolol has been used to lower portal pressure and to avoid variceal rupture and consequent hematemesis.<sup>4</sup> However, two thirds of cirrhotic patients may not respond to propranolol.<sup>4</sup>

Carvedilol is a newer non-selective  $\beta$ -antagonist which also possesses  $\alpha_1$ -antagonist receptor properties, is currently a mainstay in the treatment of heart failure and hypertension. It is 2-4 times powerful as compared to propranolol in its  $\beta$ -blocking properties.<sup>5</sup>

Color flow Doppler ultrasound is an alternate device to assess the portal pressure by waveform and damping index in the right hepatic vein.

The hepatic vein shows a triphasic waveform in normal individuals on Doppler ultrasound which is a variation of central venous pressure (CVP) of the cardiac cycle. The triphasic wave has two negative and one positive deflection as compared to the CVP, which has three positive and two negative waves.<sup>6,7</sup>

The maximum velocity and minimum velocity of downward hepatic vein flow at right hepatic vein are

measured in longitudinal scanning planes and damping index (DI) is calculated by determining minimum velocity/maximum velocity of downward hepatic flow.<sup>7</sup>

The hepatic vein flow dynamics are altered in various physiological and pathological conditions. Normal variations occur due to changes in the intra-thoracic and intra-abdominal pressures. Right-sided heart failure as a result of tricuspid insufficiency, cor-pulmonale or rhythm disturbances may show as abnormal wave forms.<sup>7</sup>

Cirrhosis of the liver results in loss of compliance in hepatic veins and leads to portal hypertension and may reflect as biphasic or monophasic waves which are essentially abnormal and indicate moderate to severe portal hypertension respectively (HVPG 12-15 mmHg).<sup>6,9,10</sup> The cause of changes in Doppler waveform may be due to the thin hepatic vein wall, which is surrounded by liver parenchyma and its compliance can be affected by increased portal pressure as a result of fibrosis (cirrhosis). Other causes include fatty infiltration,<sup>6</sup> portal vein and splenic vein thrombosis and space occupying lesion in and around the hepatic vein.

The object of this study was to assess the effect of Carvedilol in reducing portal pressure evaluated noninvasively the rough Doppler ultrasound of hepatic vein waveform and damping index (DI).

#### METHODOLOGY

This quasi-experimental study was conducted by the Department of Medical ICU, JPMC in collaboration with The Department of Radiology and Imaging JPMC, over a period of 6 months i.e. 1st June 2008 to 30th November 2008. Patients with clinical signs of cirrhosis and portal hypertension were entered into the study after a written consent. Due permission was obtained from the Ethics Committee of the Hospital to conduct this study. Patients with history of bronchial asthma, Insulin dependent Diabetes mellitus (IDDM), congestive heart failure (CHF), hepato-renal syndrome (HRS), pregnant females and those with portal vein thrombosis were excluded from the study. Patients who had a recent history of hematemesis, were hemodynamically stabilized before inducting into the study. Investigations including blood picture, liver function tests (LFT's), serum electrolytes, PT/INR and urinalysis were performed. All patients underwent an abdominal US and an upper GI endoscopy. Doppler ultrasounds of all patients were performed. The right hepatic vein was the main focus. The damping index was also calculated by dividing the minimum by maximum flow-velocities of downward HV flow at the right hepatic vein in longitudinal scanning planes (Figures 1 and 2).

Doppler ultrasound was conducted after 8 hours fasting on patients by an expert sonologist using a VOLUSION 730 PRO-V, Kretz Austria Doppler machine with a 3.5 MHz convex probe. All recordings were done in supine



 
 Figure 1: Monophasic waveform – before Carvedilol.
 Figure 2: Triphasic waveform – after Carvedilol.

position with probe in the right intercostal spaces in longitudinal axis, patient holding his/her breath in end expiration for at least 5 seconds. The sample volume was 4-5 mm with an angle of  $< 55^{\circ}$ . The right hepatic vein was identified at a distance of 3-5 cms from the junction of hepatic vein with inferior vena cava and waveforms were obtained. These waveforms were classified as monophasic (flat - without flutter), monophasic to biphasic (flat and with flutter), biphasic (no reversed flow, decreased phasic oscillation), biphasic to triphasic (normal phasic oscillations yet no flow reversal) and triphasic (reversed flow in at least one phase).7-9 After the initial baseline Doppler examination, patients were given Carvedilol 6.25 mg orally once daily for 3 days. This dose was increased to 12.5 mg once daily from the 4th day onwards till the end of 4 weeks. Patients were admitted during the first 3 days and closely observed for any side effects like bronchospasm or hypotension. They were discharged home and a week's supply of Carvedilol tablets was provided to each patient. The patients were then reviewed weekly in the out-patients department and their supply of tablets was checked to assess patient compliance. Those who showed non-compliance were dropped from the trial. At the end of 4 weeks, re-assessment by color flow Doppler was performed to see any change in wave form and the damping index was again calculated. Responders were described as those patients who showed a positive change in wave forms or a decrease of 0.10 or more in DI. Non-responders were those who showed no changes either in wave forms or an increase in the DI.

The data was analyzed on SPSS 12.0 version. The damping indices of each patient before and after administration of Carvedilol were evaluated and compared by a Paired t-test. Doppler ultrasound wave forms before and after treatment with Carvedilol were compared by Wilcoxon Signed Ranks Test. A p-value of 0.05 or less was considered as statistically significant.

#### RESULTS

Out of 65 patients entering the study including 51 males and 14 females with ages ranging from 23-70 years, (mean 47.4 years) 47 completed the 4 weeks trial, 33 of whom were males and 14 females, (78.5% vs. 21.5%). All of them had varying degrees of cirrhosis and portal hypertension and were stratified into class A (23 patients), class B (16 patients) and class C (8 patients) according to the Child-Pugh scoring system. The number of HCV +ve patients was 32 (68.1%), HBV +ve 6 patients (12.7%) and HCV/HBV co-infected patients were 2 (4.25%). Six patients (12.7%) did not have seropositivity for HCV, HBV /HDV and were classified as having cryptogenic cirrhosis.

Nine patients were lost to follow-up and non-compliance to treatment, while 4 patients were excluded due to sideeffects of bronchospasm and hypotension. Five patients (all males) died during the study (2 due to recurrence of bleeding from esophageal varices and hepato-renal syndrome occuring in 3 patients).

Six patients out of the 47 participating in the study developed minor side effects. Three of them developed nausea and vomiting which were managed in the ward; 2 suffered from loss of libido and one developed shortness of breath who were managed in the follow-up clinic.

The mean damping index, before Carvedilol was  $0.62\pm0.22$ , and after Carvedilol was  $0.49\pm0.21$  (95% Cl 0.05-0.21, t=2.9304, p=0.0043. Similarly, the mean rank of the wave form analysis after Carvedilol versus waveform before Carvedilol was 15.7 and 12.98 respectively (p=0.01) which was statistically significant as well (Table I).

 
 Table I: Change in damping index and DUS waveform before and after Carvedilol in liver cirrhosis patients.

| Damping Index     | n        | Mean <u>+</u> SD   | Mean pair<br>difference | 95% CI of the difference | p-value   |
|-------------------|----------|--------------------|-------------------------|--------------------------|-----------|
| Before Carvedilol | 47       | 0.62 <u>+</u> 0.22 | 0.13 <u>+</u> 0.26      | 0.05 - 0.21              | t= 2.9304 |
| After Carvedilol  | 47       | 0.49 <u>+</u> 0.21 |                         |                          | p=0.0043  |
| Waveform          | Ranks    | N                  | Mean rank               | Sum of ranks             | p-value   |
| Wavefrom after    | Negative | 5 a                | 15.7                    | 78.5                     | Z= 2.61   |
| Carvedilol vs.    | ranks    |                    |                         |                          |           |
| Waveform before   | Positive | 21 b               | 12.98                   | 272.50                   | p=0.01    |
| Carvedilol        | ranks    |                    |                         |                          |           |
|                   | Ties     | 21 c               | Wilcoxon rank test      |                          |           |
|                   | Total    | 47                 |                         |                          |           |

a Wavefrom after Carvedilol < Waveform before Carvedilol.

b Wavefrom after Carvedilol > Waveform before Carvedilol.
 c Wavefrom after Carvedilol = Waveform before Carvedilol

On assessment of DUS waveform as per classification described earlier, improvement after 4 weeks on carvedilol was seen in 25 (53%) patients (Table II), no change in16 (34%) while 6 (12%) suffered deterioration (Table II). Calculation by DI revealed improvement in 30 (63%) patients, no change in 10 (21%) and deterioration in 7 (14%) as depicted in Table II.

| Table II: | Comparative | analysis of | waveform | vs.   | DI.         |
|-----------|-------------|-------------|----------|-------|-------------|
| 10010 11. | oomparativo | analyoid of |          | • • • | <b>D</b> 1. |

| Parameter     | Improvement | Deterioration | No change  |  |  |  |
|---------------|-------------|---------------|------------|--|--|--|
| Waveform      | 25 (53%)    | 06 (12.7%)    | 16 (34%)   |  |  |  |
| Damping index | 30 (63.8%)  | 7 (14%)       | 10 (21.2%) |  |  |  |

## DISCUSSION

The standard method of determining the portal pressure involves insertion of a Swanz-Ganz catheter in the hepatic vein via the femoral vein and measuring the free and wedged pressures. The hepatic vein pressure gradient (HVPG) is calculated by subtracting the free pressure from the wedged pressure. The normal HVPG is 3-6 mmHg in healthy individuals.<sup>2,9</sup> Gastric and esophageal varices are formed when HVPG exceeds 10-12 mmHg. There is compelling evidence that lowering HVPG to below 12 mmHg or decreasing the pressure by 20% of baseline values results in decreased frequency of hematemesis due to variceal hemorrhage. However, this being an invasive procedure, is not well tolerated by patients and repeated measurements of HVPG cannot be performed without discomfort and risk to the patients.

Doppler ultrasound is a non-invasive alternate tool for assessing portal pressure used by other investigators before. In a Korean study conducted in 2006 the waveform in right hepatic vein on Doppler ultrasound before and after administration of terlipressin intravenously was seen.<sup>6</sup> There was positive correlation between waveform and hepatic vein pressure gradient (HVPG). A normal person showed triphasic waveform of hepatic vein (HV) and in a cirrhotic patient monophasic or biphasic waveform of HV was seen.9,10 When HVPG increased the waveform became flat. Monophasic waveform in HV was associated with severe portal hypertension HVPG > 15 mmHg with relatively high sensitivity and specificity.<sup>6</sup> This is a qualitative analysis of HV waveform but this method has limitations in evaluating response to drug therapy. This study was modified by the same investigators to assess damping index (DI) of waveforms which gave guantification of the extent of the abnormal HV waveform (loss of pulsatility) and correlation between DI and HVPG was evaluated and change was induced by intake of the drug propranolol for 3 months.7,11

International studies have employed various drugs to reduce portal pressure. These include  $\beta$ -blockers e.g. propranolol.<sup>12</sup> Later other drugs such as mononitrates, octreotide, terlipressin, captopril and more recently nonselective  $\alpha$  and  $\beta$ -blocking drug like carvedilol have been used to avoid complications of portal hypertension.<sup>2</sup>

Generally, Carvedilol studies have either been singledose or multi-dose trials to evaluate its efficacy. In one single-dose study employing a dose of 25 mg of Carvedilol, one hour after administration, the reduction in HVPG was 10% or more in 81% of patients.<sup>14</sup> A subsequent study on 10 patients reported HVPG reductions of more than 20% in 50% of the studied patients.<sup>15,16</sup> In most of the trials comparing efficacy of Carvedilol vis-à-vis propranolol, results have been in favour of Carvedilol.

Multi-dose studies usually have been extensions of single-dose studies. In one study 10 patients who completed 12.5-25 mg of Carvedilol daily, at the end of 4 weeks period had a mean HVPG reduction of 16% from the baseline.<sup>17</sup>

Another multiple-dose study involved 51 patients with cirrhosis and esophageal varices; all had baseline HVPG values greater than 12 mmHg. HVPG reduction was 20% or to less than 12 mmHg in 58% of Carvedilol treated patients versus 23% of propranolol treated patients (p < 0.05).<sup>18</sup> This study showed a reduction in portal pressure in 63.8% patients taking Carvedilol.

Since, this study was based on non-invasive and indirect measurement, larger trials to assess the efficacy of the medicine as well as the measurement tool are warranted.

#### **CONCLUSION**

Carvedilol is safe and effective in reducing portal pressure of cirrhotic patients, as measured by the damping index of hepatic waveform by Doppler ultrasonography.

#### REFERENCES

- Krige JE, Beckingham IJ. ABC of diseases of liver, pancreas and biliary system. Portal hypertension -1: varices. *BMJ* 2001; 322:348-51.
- Bosch J, Garcia-Pagan JC. Pathophysiology of portal hypertension and its complications. In: Bircher J, editor. Oxford textbook of clinical hepatology. 2nd Ed. New York. Oxford University Press; 1999. p. 653-60.
- Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites and spontaneous bacterial peritonitis. *Gastroenterology* 2001; 120:726-48.
- Boyer TD. Pharmacologic treatment of portal hypertension: past, present and future. *Hepatology* 2001; 34:834-9.
- Hemstreet BA. Evaluation of Carvedilol for the treatment of portal hypertension: *Pharmacotherapy* 2004; 24:94-104.
- Baik SK, Kim JW, Kim HS, Kwon SO, Kim YJ, Park JW, et al. Recent variceal bleeding: Doppler US hepatic vein waveform in assessment of severity of portal hypertension and vasoactive drug response. *Radiology* 2006; **240**:574-80. Comment in: p. 309-10.

- Kim MY, Baik SK, Park DH, Lim DW, Kim JW, Kim HS, *et al.* Damping index of Doppler hepatic vein waveform to assess severity of portal hypertension and response to propranolol in liver cirrhosis: a prospective non-randomized study. *Liver Int* 2007; 27:1103-10.
- 8. Dietrich CF, Lee JH, Gottschalk R, Herrmann G, Sarrazin C, Caspary WF, *et al.* Hepatic and portal vein flow pattern in correlation with intrahepatic fat deposition and liver histology in patients with chronic hepatitis C. *AJR Am J Roentgenol* 1998; **171**:437-43.
- 9. Bolondi L, Li Bassi S, Gaiani S, Zironi G, Benzi G, Santi V, *et al.* Liver cirrhosis: changes of Doppler waveforms of hepatic veins. *Radiology* 1991; **178**:513-6.
- 10. Colli A, Cocciolo M, Riva C, Martinez E, Prisco A, Pirola M, *et al.* Abnormalities of Doppler waveform of the hepatic veins in patients with chronic liver disease: correlation with histological findings. *AJR Am J Roentgenol* 1994; **162**:833-7.
- 11. Kokt, Haagsma EB, Klompmaker IJ. Doppler ultrasound of the hepatic artery and vein performed daily in the first two weeks after orthotropic liver transplantation. Useful for the diagnosis of acute rejection? *Invest Radiology* 1996; **31**:173-9.
- D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis* 1999; **19**:475-505.
- Baik SK, Park DH, Kim MY, Choi YJ, Kim HS, Lee DK, *et al.* Captopril reduces portal pressure effectively in portal hypertensive patients with low portal venous velocity. *J Gastroenterol* 2003; **38**:1150-4.
- 14. Forrest EH, Bouchier IA, Hayes PC. Acute haemodynamic changes after oral carvedilol, a vasodilating beta-blocker, in patients with cirrhosis. *J Hepatol* 1996; **25**:909-15.
- 15. Stanley AJ, Therapondos G, Helmy A, Hayes PC. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. *J Hepatol* 1999; **30**:479-84.
- Tripathi D, Therapondos G, Lui HF, Stanley AJ, Hayes PC. Haemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating beta-blocker, in patients with cirrhosis and portal hypertension. *Aliment Pharmacol Ther* 2002; 16:373-80.
- Bañares R, Moitinho E, Matilla A, García-Pagán JC, Lampreave JL, Piera C, *et al.* Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. *Hepatology* 2002; 36:1367-73.