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Changes in Doppler Ultrasound Indices of Hepatic Circulation after Treatment with Beta Blockers: A Pilot Study

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ABSTRACT

Background: Portal hypertension is a serious complication of liver cirrhosis. Doppler ultrasound assessment may be a non-invasive and cost-effective means of evaluating portal hemodynamics in patients with portal hypertension. **Aims & objectives:** To assess efficacy of Doppler ultrasound in detecting changes in hemodynamics of hepatic circulation after beta-blocker administration. **Methodology:** 11 patients with liver cirrhosis and portal hypertension were included. All underwent Doppler assessment of portal vein velocity (PVV), spleno-portal index (SPI), congestive index (CI), liver vascular index (LVI), dampening index (DI), hepatic artery velocity (HAV), splenic artery velocity (SAV), hepatic artery resistive index (HARI) and splenic artery resistive index (SARI). They were started on beta-blocker carvedilol 6.25 mg once daily and recalled after two weeks for repeat assessment. **Results:** Out of 13 enrolled, 4 were lost to follow up and one stopped carvedilol. 8 remained. The changes in parameters were: PVV: reduction in 3 (37.5%), no change in 1 and increase in 4(50%) patients; SPI: reduction in 3 (37.5%) and increase in 5 (62.5%); CI: reduction in 3 (37.5%), no change in 1 and increase in 4 (50%); LVI: decrease in 3 (50%), no change in 1 and increase in 2; DI: decrease in 5 (62.5%) and increase in 3 (37.5%); HAV: increase in 4 (50%), no change in 1 (12.5%) and decrease in 3 (37.5%); SAV: decrease in 4 (50%) & increase in 4 (50%); HARI: increase in 7 (87.5%) and decrease in 1 (12.5%); SARI: reduction in 3 (37.5%) and increase in 3 (37.5%). 3 patients achieved reduction in 5 (PVV, LVI, DI, SARI & SAV) parameters. DI had the largest number of patients with observable reduction and HARI with the largest number showing observable increase in measured parameters. **Conclusion:** Doppler ultrasound represents a cost effective means of assessing the hemodynamics of hepatic circulation and any associated changes due to diseases and drugs.

Keywords: Portal hypertension, Doppler ultrasound parameters, Beta-blockers, Carvedilol, Non-invasive assessment of portal hypertension

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INTRODUCTION

Cirrhosis of liver is amongst the leading cause of mortality and morbidity worldwide. Development of esophageal varices is one of the major complications of portal hypertension.[1] Its prevalence varies from 20-30% in patients with cirrhosis.[2] After varices have developed, one third of all patients die of bleeding from varices.[3]

Baveno VI consensus conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of esophageal varices.[4] The Baveno VI consensus also recommends the use of drugs that lower portal pressure during episodes of variceal bleeding and also as secondary prophylaxis once bleeding has been controlled. Vasoactive agents to lower portal pressure during episodes of bleeding include octreotide and terlipressin. Agents for secondary prophylaxis are mainly beta-blockers such as propranolol, nadolol and carvedilol. These agents serve to reduce portal pressure.

Assessment of hemodynamics of the portal and associated circulation using Doppler ultrasound is a

non-invasive technique.[5] Indices of Doppler ultrasound like portal vein diameter andvelocity; splenic vein diameter and splenic resistance index have shown some promise regarding non-invasive prediction of esophageal varices.[6,7,8] In addition to these, other parameters measured by Doppler ultrasound include congestion index,[9] dampening index,[10] liver vascular index,[11] resistive and pulsatile indices,[12,13] spleno-portal index[14] and the pulsatility index.[15] Cirrhosis of liver leads to increase in the diameter of portal vein while the velocity of blood flow is decreased. The "congestion index" means the ratio between the cross-sectional area (cm^2) and the blood flow velocity (cm/sec) of the portal vein, determined by a Doppler system. It is suggested that the congestion index reflects the pathophysiological hemodynamics of the portal venous system in portal hypertension. The congestion index of the portal vein is increased in cirrhosis. Among cirrhotic patients, those with history of esophageal variceal bleed had a significantly greater mean flow volume in the splenic vein, greater mean splenic vein/portal trunk diameter and greater mean spleen size compared with the non-bleeder. Although direct measurement of the hepatic venous pressure gradient is considered the gold standard in measuring the degree of portal hypertension, it is invasive and expensive. Accurate measurement of degree of portal hypertension is necessary in the management and monitoring of patients with liver cirrhosis by assessing the efficacy of therapeutic agents as well as staging liver disease and risks of procedures (such as hepatic lobar resection for hepatocellular carcinoma). Among therapeutic agents, the efficacy of pharmacological agents such as beta-blockers that are meant to reduce portal pressure is an important aspect.[10,16] Carvedilol is one such beta-blocker that has been proven to reduce portal pressure in various studies and is now recognized as a standard treatment for patients with portal hypertension.[17-20]

If Doppler studies can be proven to be accurate in measuring the effect of such agents on portal circulation, then they can be a simpler and cost effective alternative to HVPG measurement. This method is not without its problems. Operator skill and experience along with clearly defined parameters are mandatory for uniform results. Thus, to date, utilizing Doppler ultrasound as a non-invasive assessment of hemodynamics, in patients with portal hypertension, has not always proved reliable and some studies have clearly hinted at this.[21,22] Our study aims to see how Doppler ultrasound detects changes in parameters of hepatic circulation before and after treatment with the beta-blocker carvedilol. If definitive changes are noted, it would open further avenues of study. These would especially include studies where Doppler ultrasound can be used as a non-invasive means of assessing the degree of portal hypertension as well as effect of drugs and procedures aimed at reducing portal pressure.

Objectives

To assess the efficacy of Doppler ultrasound in measuring changes to parameters of hepatic circulation during therapy with carvedilol.

Operational definitions

1. **Portal Vein Velocity:** Peak venous velocity in portal vein cm/s
2. **Splenic Index:** Splenic length x Splenic width
3. **Spleno-Portal Index:** Ratio of splenic index to portal vein velocity
4. **Dampening Index:** Ratio of minimum hepatic vein velocity to the maximum hepatic vein velocity
5. **Congestion Index:** Ratio ofportal vein area to portal vein velocity
6. **Resistive Index:** It is a measure of pulsatile blood flow that reflects the resistance to blood flow caused by microvascular bed distal to the site of measurement.RI is measured as (S − D)/S, where **S** is the height of the systolic peak and **D** is the height of the end-diastolic trough
7. **Pulsatility Index:** Is equal to the difference between the peak systolic velocity and the minimum diastolic velocity divided by the mean velocity during the cardiac cycle
8. **Liver Vascular Index:** Portal vein velocity / Hepatic artery Pulsatility Index
9. **Splenic Artery Resistive Index:** It is the difference between the peak and minimum systolic velocity divided by the systolic velocity
10. **Splenic Artery Pulsatility Index:** Difference between the peak systolic velocity and the minimum diastolic velocity divided by the mean velocity
11. **Hepatic Artery Resistive Index:** It is the difference between the peak and minimum systolic velocity divided by the systolic velocity
12. **Hepatic Artery Pulsatility Index:** Difference between the peak systolic velocity and the

minimum diastolic velocity divided by the mean velocity

METHODOLOGY

Study design: Prospective interventional pilot study

Setting: Departments of Gastroenterology and Radiology, Shaikh Zayed Hospital, Lahore

Duration: 1 month

Sample size: A sample size of 13 patients was considered as a pilot group

Inclusion criteria:

- All adult patients of either sex with liver cirrhosis and evidence of portal hypertension confirmed by presence of varices on esophagogastroduodenoscopy

Exclusion criteria:

- Patients with any contraindication to the use of beta-blockers
- Patients with portal venous thrombosis
- Patients with hepatic venous thrombosis

Data collection procedure:

The study was started after obtaining informed consent of all patients included in the study. All patients of both sexes, aged 18 years and above, with a confirmed history of liver cirrhosis and portal hypertension as evidenced by presence of specific findings on abdominal ultrasound (coarse, shrunken liver, splenomegaly and dilated portal vein) and upper GI endoscopy (esophageal and/or gastric varices) were included in the study. Since use of carvedilol is part of the standard treatment of all patients with lover cirrhosis and portal hypertension, any special ethical permission was not required.

13 patients were enrolled. The patients underwent Doppler ultrasound to assess portal vein velocity (PVV), spleno-portal index (SPI), congestive index (CI), liver vascular index (LVI), dampening index (DI), hepatic artery velocity (HAV), splenic artery velocity (SAV), hepatic artery resistive index (HARI) and splenic artery resistive index (SARI). The patients were then started on beta-blocker therapy in the form of carvedilol at a dose of 6.25 mg once daily. The patients were recalled after two weeks to undergo repeat Doppler ultrasound with measurement of the same parameters. All findings were collected through a specially designed proforma.

Data analysis: Variables including age, sex, and Doppler indices were assessed through a specially designed proforma. Data was analyzed using SPSS 22.

Ethical considerations:

1. Written and informed consent was obtained from all patients.
2. Beta-blockers such as carvedilol are routinely prescribed as part of secondary prophylaxis against variceal bleeding.

RESULTS

Out of the 13 patients initially enrolled, 4 did not return for their follow up ultrasound and one had stopped taking carvedilol. 8 patients underwent Doppler ultrasound before and after carvedilol therapy. 5 were male and 3 female. Average age was 52.5 years. Cause of liver disease was HCV in 7 and HBV in one patient. The changes in parameters measured were as follows:

PVV: Reduction seen in 3 (37.5%) patients, no change noted in 1 patient and increase seen in 4 (50%) patients (Table A)

SPI: Reduction seen in 3 (37.5%) patients and increase seen in 5 (62.5%) patients (Table B)

CI: Reduction seen in 3 (37.5%) patients, no change noted in 1 patient and increase seen in 4 (50%) patients (Table C)

LVI: Decrease seen in 4 (50%) patients and increase in 4 (50%) patients (Table D)

DI: Decrease noted in 5 (62.5%) patients and increase noted in 3 (37.5%) patients (Table E)

HAV: Increase noted in average measured velocities in 4 (50%) patients, no change noted in 1 (12.5%) and decrease noted in average measured velocities in 3 (37.5%) patient (Table F)

SAV: Decrease in average measured velocities noted in 4 (50%) patients. Increase noted in average measured velocities in 4 (50%) patients (Table G)

HARI: Increase noted in 7 (87.5%) patients and decrease in 1 (12.5%) patient (Table H)

SARI: reduction seen in 3 (37.5%) patients, increase seen in 3 (37.5%) and no change in 2 (25%) patients (Table I).

3 patients achieved reduction in 5 parameters (PVV, LVI, DI, SARI& SAV). One patient achieved reduction in 4 parameters (SPI, CI, DI & SARI). DI was the one parameter associated with the largest number of patients, 5 (62.5%), showing observable reduction after carvedilol therapy and HARI with the largest number, 7 (87.5%) showing observable increase.

Table A: Changes in portal vein velocity after 2 weeks of carvedilol

Patient Serial No.	Portal Vein Velocity (PVV) cm/sec	
	Pre-carvedilol	Post-carvedilol
1	21.13	21.13
2	24.7	**22.9**
3	31.75	**22.93**
4	14.11	21.17
5	31.52	33.85
6	15.88	17.64
7	7.9	10
8	15	**12**

Table B: Changes in spleno-portal index after 2 weeks of carvedilol

Patient Serial No.	Spleno-portal index (SPI)	
	Pre-carvedilol	Post-carvedilol
1	3	3.4
2	2.44	3.24
3	2.62	4.98
4	5.3	**3.6**
5	3.559	4.7
6	51.7	**42.8**
7	6.86	**5.421**
8	5.86	6.25

Table C: Changes in congestive Index after 2 weeks of carvedilol

Patient Serial No.	Congestive Index (CI)	
	Pre-carvedilol	Post-carvedilol
1	0.06	0.08
2	0.05	0.065
3	0.059	0.074
4	0.087	**0.05**
5	0.041	0.044
6	0.072	**0.069**
7	0.16	**0.14**
8	0.15	0.15

Table D: Changes in liver vascular index after 2 weeks of carvedilol

Patient Serial No.	Liver Vascular Index (LVI)	
	Pre-carvedilol	Post-carvedilol
1	20.12	**18.05**
2	23.3	**19.57**
3	33.07	**20.11**
4	15.34	19.6
5	23.176	25.45
6	14.84	14.9
7	2.92	4.5
8	13.04	**10.34**

Table E: Changes in dampening index after 2 weeks of carvedilol

Patient Serial No.	Dampening Index (DI)	
	Pre-carvedilol	Post-carvedilol
1	0.46	0.74
2	0.60	**0.369**
3	0.12	**0.04**
4	0.68	0.687
5	0.46	**0.29**
6	0.73	**0.53**
7	0.2	4
8	0.36	**0.18**

Table F: Changes in mean hepatic artery velocity after 2 weeks of carvedilol

Patient Serial No.	Mean Hepatic Artery Velocity (HAV) cm/sec	
	Pre-carvedilol	Post-carvedilol
1	39.26	47.65
2	51.15	51.15
3	23.815	40.42
4	22.9	36.15
5	35.6	**35**
6	22.93	34.4
7	31	**22**
8	19	**15**

Table G: Changes in mean splenic artery velocity after 2 weeks of carvedilol

Patient Serial No.	Mean Splenic Artery Velocity (SAV) cm/sec	
	Pre-carvedilol	Post-carvedilol
1	39.45	82.2
2	96.2	**60.5**
3	103.25	**96.25**
4	65.25	**58.65**
5	92.2	117.4
6	57.33	86.4
7	12.7	39
8	62	**32**

Table H: Changes in hepatic artery resistive index after 2 weeks of carvedilol

Patient Serial No.	Hepatic Artery Resistive Index (HARI)	
	Pre-carvedilol	Post-carvedilol
1	0.6	0.68
2	0.68	0.738
3	0.65	0.72
4	0.63	0.7
5	0.67	0.8
6	0.7	0.74
7	0.6	0.79
8	0.75	**0.7**

Table I: Changes in splenic artery resistive index after 2 weeks of carvedilol

Patient Serial No.	Splenic Artery Resistive Index (SARI)	
	Pre-carvedilol	Post-carvedilol
1	0.6	0.67
2	0.676	**0.584**
3	0.5647	**0.53**
4	0.58	0.75
5	0.6	0.61
6	0.7	**0.63**
7	0.6	0.6
8	0.8	0.8

DISCUSSION

This was a small study intended as a pilot project. Nevertheless it highlights the definite changes noted in hepatic and splenic circulation after administration of a pharmacologic agent that is specifically meant to reduce portal pressure. Our observations show that dampening index (DI) was the one parameter noted to have the most consistent reduction among all others. Also, almost all patients were seen to have increased mean hepatic and splenic artery velocities (HAV & SAV, respectively) following carvedilol therapy (except the single patient with reduction in SAV). Ideally, these findings need confirmation with HVPG measurement in order to identify specific Doppler parameters that correlate directly with HVPG. As stated earlier, HVPG is expensive to measure and an invasive procedure. At our centre, HVPG measurement on average costs approximately$700. Doppler ultrasound is noninvasive and costs $10. Larger trials may include correlation of Doppler parameters with size of esophageal varices and degree of hepatic fibrosis as seen on shear wave elastography. Other trials can utilize higher doses of carvedilol. This may result in identification of specific parameters (in addition to the dampening index) that show direct correlation with severity of liver disease and portal hypertension and changes to the latter in response to drugs. These parameters will aid in making prognostic decisions, risk assessment and assessment of efficacy of therapeutic drugs and procedures.

CONCLUSION

Doppler ultrasound represents a cost effective means of assessing the hemodynamics of hepatic circulation and any associated changes due to diseases and drugs.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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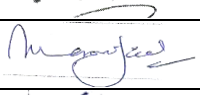
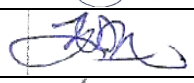
Dr. Muhammad Israr ul Haq	Contributions to experimental conception and design	
Dr. Masood Javed	Drafting the article & revising it critically for important intellectual content	
Dr. Faisal Ehsan Cheema	Acquisition, analysis and/or interpretation of data	
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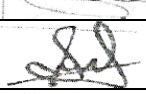
Dr. Aamir Khan	Acquisition, analysis and/or interpretation of data	
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