Original Article

Correlation of Hepatic Artery Resistive Index with Portal Pressure and Serum Nitric Oxide Levels in Patients with Extrahepatic Portal Vein Obstruction

Abhishek Gupta, Veereshwar Bhatnagar, Anjan Kumar Dhua, Manisha Jana[1], Archana Singh[2], Rohan Malik[3]

Departments of Pediatric Surgery, [1]Radiodiagnosis, [2]Biochemistery and [3]Pediatrics, All India Institute of Medical Sciences, New Delhi, India

Abstract

Aim: The aim was to study the correlation of hepatic artery resistive index (HARI) with the portal pressure (PP) and its surrogate marker serum nitric oxide (NO) levels and to determine the validity of HARI as noninvasive indirect marker of PP in extrahepatic portal venous obstruction (EHPVO) pre- and postoperatively.

Methods: A prospective study was conducted on 19 patients with EHPVO undergoing proximal lienorenal (LR) shunt or devascularization from February 2016 to January 2018. HARI, calculated from Doppler sonography, and NO were measured preoperatively and 14, 30 and 90 days postoperatively. Intraoperatively, PP was measured before splenectomy, and both PP and NO were measured postshunt.

Results: Mean age was 10.58 ± 2.85 years, and male:female ratio was 15:4. LR shunt was done in 16 while three patients required devascularization. There was a significant fall in the HARI (0.06 ± 0.02, $P = 0.02$), NO (14.31 ± 2.66 μmol/l, $P < 0.001$), and PP (11.81 ± 1.03 mmHg, $P < 0.001$) following shunt surgery. However, fall in HARI did not correlate with fall in PP. Preoperative HARI also did not correlate with preshunt/devascularization PP nor with preoperative NO. Postoperatively, HARI did not correlate with NO at 14-, 30-, and 90-day follow-up.

Conclusion: HARI bears no correlation with PP or NO. Hence, it cannot be used as an indirect marker of PP.

Keywords: *Extrahepatic portal venous obstruction, hepatic artery resistive index, nitric oxide, portal pressure*

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Introduction

Extrahepatic portal vein obstruction (EHPVO) is the most important cause of prehepatic portal hypertension (PHT) in children. It involves the occlusion of the main trunk of the portal vein, which gets replaced by a series of small collateral veins giving the appearance of portal cavernoma. The most common acquired reasons are omphalitis, instrumentation, and cannulation of the umbilical vein at birth such as umbilical vein catheterization, sepsis, and dehydration in infancy.

The most common presenting symptom of EHPVO is upper gastrointestinal bleed from esophageal varices. After clinical stabilization of the patient, abdominal ultrasonography (USG) is the first imaging study done which readily recognizes the cavernous transformation of the portal vein and the underlying portal vein thrombosis. However, unlike in other causes of PHT, it does not give us much information on hemodynamics of portal vein due to its cavernous transformation,[1] as a result of which we do not have a reliable noninvasive indicator of PHT and its severity in EHPVO patients as yet. Hepatic artery indices are likely to be more informative under such circumstances.[2]

Address for correspondence: Dr. Veereshwar Bhatnagar, Room No. 4002, Department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi, India.
E-mail: veereshwarb@hotmail.com

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Definitive management of EHPVO involves the creation of a portosystemic shunt to decompress the portal venous system, which subsequently alleviates portal hypertension and resulting symptoms from the same. Serum nitric oxide (NO) levels have been shown to be a surrogate marker for portal hypertension in previous studies conducted at this institute in cases of EHPVO,[3] extrahepatic biliary atresia (BA),[4] as well as choledochal cyst.[5] However, the test is invasive and not readily available.

The present study was conducted to find a correlation of hepatic artery resistive index (HARI) with intraoperatively measured portal pressure (PP) in patients of EHPVO as well as serum NO levels measured postoperatively, in an attempt to find noninvasive and reproducible marker of portal hypertension in these patients.

Materials and Methods

This prospective study was conducted on a total of 19 patients of EHPVO who underwent surgical intervention in the Department of Pediatric Surgery, All India Institute of Medical Sciences, over a period of 2 years (February 2016–January 2018). Institute ethical committee clearance (No. IECPG/160/1/2016) was obtained before the initiation of the research work.

The USG with Doppler imaging in the study population was done with an advanced state of the art USG scanner using a curvilinear 2–5 MHz and a high linear frequency (7–12 MHz) probe. HARI was calculated after calculating hepatic arterial peak systolic velocity and end-diastolic velocity preoperatively (HARI0) as well as 14, 30, and 90 days postoperatively (HARI1, HARI2, and HARI3, respectively) from the following formula:

HARI = (peak systolic velocity – end-diastolic velocity)/ peak systolic velocity

NO was measured from a blood sample taken from a peripheral vein. This sample was then centrifuged to separate plasma. NO concentration (μmol/l) is measured as its stable metabolite nitrate and nitrite spectrophotometrically by the Griess reaction. Samples for NO were taken in the preoperative period (NO0), immediately after shunt (NO1) intraoperatively, and at 14, 30, and 90 days postoperatively (NO2, NO3, and NO4, respectively).

After carrying out computed tomographic portogram for assessment of the vascular anatomy, a proximal lienorenal (LR) shunt with splenectomy or devascularization was performed by the standard surgical technique by a single surgeon. Intraoperatively PP was measured by cannulating a vein in the gastroepiploic arcade with a 20G intravenous cannula and connecting it to a pressure transducer (Datex-Ohmeda S/5™ monitor) before splenectomy and after the creation of the shunt. PP was recorded by taking the mean of three readings.

Data analysis was carried out using Stata 11.0 (Stata statistical Software, StataCorp LP, College Station, TX, USA). The change in NO and HARI over 3 months from baseline was assessed using repeated measures analysis of variants. The correlation between NO, HARI, and intraoperative PP was done using Spearman's rate correlation coefficient with $P < 0.05$ which was considered as statistically significant.

Results

A total of 19 patients were included in the study, of which 14 (74%) were male and 5 (26%) were female. Mean age was 10.58 ± 2.85 years with age ranging between 5 and 14 years. Proximal LR shunt was done in 16 (84%) patients, and 3 (16%) patients were devascularized.

Mean HARI0 in patients who underwent proximal LR shunt was 0.70 ± 0.08. The mean HARI1, HARI2, and HARI3 observed in these patients (n = 14, two patients were lost to follow-up) were 0.70 ± 0.08, 0.65 ± 0.06, and 0.68 ± 0.06, respectively. Change in mean HARI over time is depicted in Figure 1.

Mean HARI0–HARI1 was 0.06 ± 0.02, which was statistically significant, P = 0.02. Subsequently, there was a rise in HARI at 30 days with the corresponding P = 0.06, almost reaching significance levels. Furthermore, the difference between HARI2 and HARI3 from the baseline became insignificant with P = 0.22 and P = 0.08, respectively.

The mean NO0 levels as measured in 14 patients (sample hemolyzed in 2 patients) who underwent

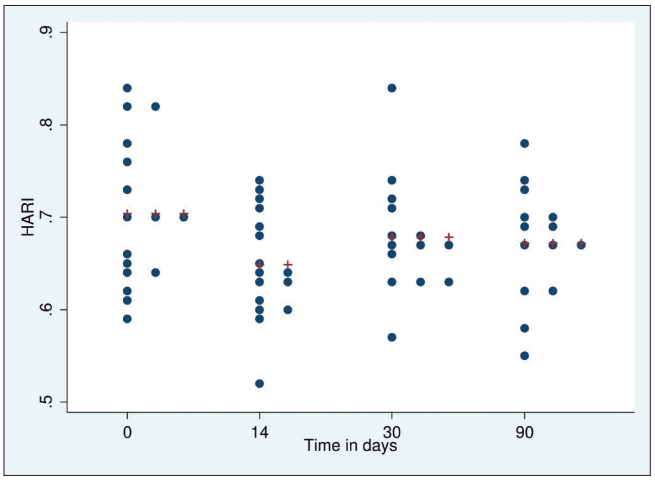

Figure 1: Change in mean hepatic artery resistive index over time in patients who underwent proximal lienorenal shunt

proximal LR shunt were 27.39 ± 10.37 µmol/l. The mean NO1 was 13.07 ± 4.28 µmol/l in these patients, and the mean fall in NO (NO0–NO1) was 14.31 ± 2.66 µmol/l, which was statistically significant, $P < 0.001$. Subsequent mean NO (NO2, NO3, and NO4) levels remained low with a significant difference from the baseline but no significant serial change. Change in NO levels over time is depicted in Figure 2.

HARI values did not show any correlation with corresponding NO value at any particular point of time with corresponding R and *P* values as shown in Table 1.

The mean P0 in LR shunt patients ($n = 16$) was 36.50 ± 6.00 mmHg. Mean P1 was 24.69 mmHg with a mean P0–P1 of 11.81 ± 1.03 mmHg, which was statistically significant, $P < 0.001$ [Table 2].

Preshunt PP (P0) did not have a significant correlation with presurgery HARI (HARI0) with $R = 0.32$ and $P = 0.18$. Fall in PP postshunt (P0–P1) also did not have a significant correlation with fall in HARI (HARI0–HARI1) with $R = 0.02$ and $P = 0.94$.

Discussion

EHPVO is an uncommon disorder, but it is the most important cause of prehepatic portal hypertension in children. USG abdomen with Doppler is the first imaging study of choice in a child presenting with features of portal hypertension such as hematemesis, splenomegaly, and abdominal distension. Additional evaluation and interventions are performed endoscopically to document varices and manage them appropriately. Although one can reliably diagnose the cavernous transformation of portal vein using USG Doppler in EHPVO cases, we still lack an indirect noninvasive marker to assess the severity of portal hypertension in these patients, as mentioned previously. Hence, in this study, we attempted to test the validity of HARI as an indirect marker for the same.

The male-to-female ratio among 19 patients was 14:5. Proximal LR shunt was done in 16 (84%), and 3 (16%) patients were devascularized. The mean preshunt PP ($n = 19$) was 36.68 ± 5.51 mmHg. The fall in PP postshunt was statistically significant with $P < 0.001$. Proximal LR shunt is a nonselective shunt which diverts blood from high-pressure portal circulation through the splenic vein to low pressure systemic circulation, i.e., left renal vein, thus lowering the PP. Similar fall in PP was noted by Goel *et al*. in a study conducted earlier.[3]

There was also a significant fall in HARI postsurgery with $P = 0.02$. This fall in HARI can be explained by the inverse relationship between the portal and hepatic arterial flows as detailed in studies by Ternberg and Butcher[6] and Lautt.[7] Ternberg and Butcher explained the phenomenon based on their experiments on mongrel dogs by the simple mechanical effect of interposing a slower-flowing stream in the path of a faster-flowing stream, whereas Lautt explained the same based on the "adenosine washout theory." This inverse relationship has also been documented in several studies in literature where portal flow was interrupted in patients with liver tumors in preparation for future hepatectomy.[8-10] However, Randhir *et al*. did not find any significant difference in HARI values in EHPVO patients being treated medically as compared to controls.[11]

In the case of EHPVO, the main portal vein is thrombosed, and the body naturally shunts blood to systemic circulation bypassing liver via portosystemic shunts, most common site of which is lower esophagus manifesting as lower esophageal varices. However, some amount of hepatopetal flow through portal circulation is maintained through venous collaterals that form around

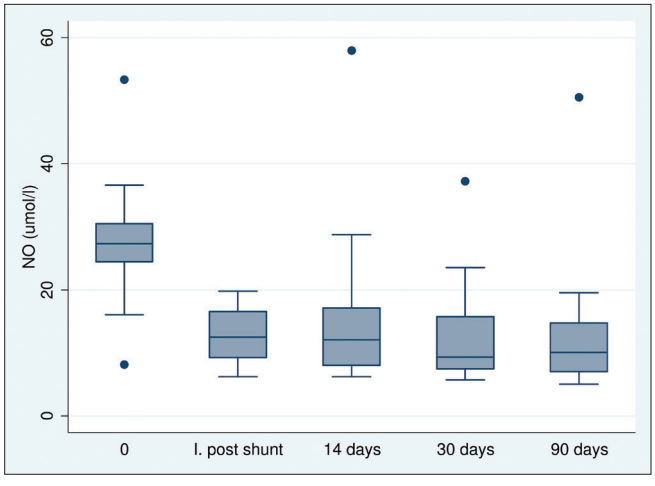

Figure 2: Change in nitric oxide values over time in patients who underwent proximal lienorenal shunt

Table 1: Correlation of hepatic artery resistive index with nitric oxide in patients who underwent proximal lienorenal shunt

HARI versus NO	*R*	*P*
HARI0 versus NO0	0.13	0.66
HARI1 versus NO2	0.19	0.51
HARI2 versus NO3	0.55	0.06
HARI3 versus NO4	−0.40	0.18

HARI: Hepatic artery resistive index, NO: Nitric oxide

Table 2: Mean intraoperative portal pressure

PP (mmHg)	LR shunt (*n*=16)	Devascularization (*n*=3)	Total patients (*n*=19)
P0	36.50±6.00	37.67±4.04	36.68±5.65
P1	24.70±7.15	31.00±2.65	-

PP: Portal pressure, LR: Lienorenal

the main portal vein that leads to the formation of portal cavernoma. The decrease in HARI in our study postsurgery may be explained by the fact that by creating a shunt, all the hepatopetal flows are reversed leading to an increase in hepatic arterial flow by lowering hepatic arterial resistance.

Another significant finding in our study was that mean HARI shows increase reaching significance levels at 30-day follow-up (P = 0.06) that ultimately leads to a difference in HARI becoming insignificant from baseline at the 30- and 90-day follow-up. It may further be explained by the possibility that some amount of hepatopetal flow is restablished over the time in the patients following shunt surgery consequent to formation of new collaterals. Hepatic arterial resistance increases subsequently leading to decreased hepatic arterial flow.

Preoperative HARI (HARI0) was not found to have any correlation with preshunt PP (P0) in our study with P = 0.18. In a study conducted by Mittal *et al*., PP was found to have a linear correlation with HARI in patients with BA.[12] Similar findings were noted by Zhang *et al*. in patients with chronic liver disease.[13] Westra *et al*. took portal vein RI as an indirect measure of PP and found it to be directly correlating to HARI.[1]

There seems to be a parallel increase in resistance of portal venous as well as hepatic arterial vasculature in patients of biliary atresia as well as cirrhosis because of distortion of hepatic parenchyma along with its contained sinusoids which, however, is not the case with EHPVO in which liver parenchyma is relatively preserved. Furthermore, the fall in PP did not correlate with fall in HARI postsurgery in our study with P = 0.94. It is clear from our research that HARI bears no correlation with PP in patients with EHPVO.

The mean fall in NO postshunt was 14.33 ± 2.66 μmol/l, which was statistically significant with P < 0.001. NO values remained low significantly with nonsignificant interval change at 14-, 30-, and 90-day follow-up. Goel *et al*. observed a similar pattern of NO values in EHPVO patients in a study conducted previously.[3] However, we could not establish any correlation between HARI and NO values both preoperatively and at subsequent follow-up. HARI is likely related to portal flow as explained above and therefore varies independently of PP and its surrogate marker NO. No study in the past has attempted to correlate HARI with NO in EHPVO patients.

A significant limitation of our study is the limited sample size as EHPVO is a relatively rare condition, and the duration of the study was limited to 2 years. Therefore, further studies with larger sample size are required to confirm the findings of the present study.

Conclusion

The present study has refined our knowledge about hepatic portal hemodynamics in patients with EHPVO. However, an attempt to find a noninvasive marker of PP remains elusive as an index based on USG Doppler studied in our study, i.e., HARI appears to bear no direct correlation with PP, and it varies by a mechanism which is independent of PP. Therefore, it can neither be used as a noninvasive marker of PP at follow-up postproximal LR shunt in EHPVO patients nor can it be used as a marker of severity of portal hypertension preoperatively.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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