Research Article

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Measurement of hepatic vein pressure gradient in children with chronic liver diseases

Roberto Miraglia[1,*], Angelo Luca[1], Luigi Maruzzelli[1], Marco Spada[2], Silvia Riva[3], Settimo Caruso[1], Giuseppe Maggiore[4], Bruno Gridelli[2], Jaime Bosch[5]

[1]*Department of Diagnostic and Interventional Radiology, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), University of Pittsburgh Medical Center, Palermo, Italy;* [2]*Department Transplantation Surgery, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), University of Pittsburgh Medical Center, Palermo, Italy;* [3]*Department of Pediatric Hepatology, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), University of Pittsburgh Medical Center, Palermo, Italy;* [4]*Division of Gastroenterology and Hepatology, Department of Pediatrics, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy;* [5]*Liver Unit, Hospital Clinic I Provincial de Barcelona and Centro de Investigacion Biomedica en Red de Enfermedades Hepaticas y Digestivas (CIBEREHD) Barcelona, Spain*

Background & Aims: The aim of this study is to present our preliminary experience with Hepatic Vein Pressure Gradient (HVPG) measurements in pediatric patients with chronic liver disease.
Methods: Institutional review board approval was obtained. HVPG was measured in 20 pediatric patients, mean age 82 ± 54 months, with chronic liver disease, without extrahepatic portal vein obstruction. In nine patients the end-stage liver disease was secondary to biliary atresia; in the remaining 11, to various causes. Eleven patients had esophageal varices at endoscopy, 14 had perigastric and periesophageal collaterals at imaging scan, three had ascites, 12 had low platelet count, and all had splenomegaly.
Results: Hepatic vein catheterization was technically possible in all patients without complications. HVPG values were elevated in all but three patients, ranging between 2 and 33 mmHg (mean 11.3 ± 7.2 mmHg), thus indicating a sinusoidal component in portal hypertension. A salient finding was the presence of hepatic venovenous shunts in 7 out of 9 patients with biliary atresia; however, the HVPG could still be measured distal to the shunts, but in three patients (with an HVPG of 8 mmHg) it was determined in an area with a small venovenous communication still visible, therefore underestimating the actual portal pressure gradient. No venovenous shunts were detected in the non-biliary atresia patients.
Conclusions: HVPG is a feasible procedure in pediatric patients. Patients with biliary atresia very frequently have communicating vessels between hepatic veins. This hitherto unacknowledged finding can lead to the underestimation of portal pressure by HVPG measurement.

Keywords: Biliary atresia; Diagnosis; Variceal bleeding; Ascites; Pediatrics.
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*Corresponding author. Address: Department of Diagnostic and Interventional Radiology, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (ISMETT), Via Tricomi 1, 90127 Palermo, Italy. Tel.: +39 3357000350; fax: +39 091 2192344.
E-mail address: rmiraglia@ismett.edu (R. Miraglia).
Abbreviations: HVPG, hepatic vein pressure gradient; FHVP, free hepatic vein pressure; WHVP, wedged hepatic vein pressure; IVVS, intra-hepatic venous–venous shunts.

Introduction

Portal hypertension is an almost unavoidable consequence of chronic liver diseases with a wide variety of complications including ascites, hepatic encephalopathy, and bleeding from gastroesophageal varices, which represent the leading causes for liver transplantation and death in adults and children with end-stage liver disease. While there are evidence-based approaches to the management of adults with portal hypertension [1–2], these are not available for children, hence making it difficult for pediatric hepatologists to determine whether recent advances in the management of portal hypertension in adults can be extrapolated to pediatric patients [3].

Portal pressure, in chronic liver diseases, is commonly measured by the hepatic venous pressure gradient (HVPG), defined as the difference between wedged (occluded) and free hepatic venous pressures with normal values ranging between 1 and 5 mmHg. In adult patients with cirrhosis, this measurement has been shown to be reproducible and the best predictor of the complications of portal hypertension [4–5]. It is well known that varices, variceal bleeding, portal hypertensive gastropathy, and ascites do not occur until the HVPG increases above 10 mmHg, a pressure threshold defining clinically significant portal hypertension. Moreover, a reduction in HVPG of $\geqslant$20% from baseline or a final HVPG $\leqslant$12 mmHg, has been shown to result in a reduction of the complications of cirrhosis and improved survival [6] in studies where HVPG monitoring has been used to assess target reductions of portal pressure during secondary and primary pharmacological prophylaxis of variceal bleeding [5–10].

In children the high prevalence of extrahepatic portal vein obstruction, which causes pre-hepatic portal hypertension, diminishes the applicability of HVPG, but no studies have been performed in pediatric patients with advanced chronic liver diseases with regards to the applicability of HVPG in assessing and

managing portal hypertension. A difficulty for the clinical use of these studies in children is the need for sedation or general anesthesia which adds considerable costs to patient management; however, this limitation applies to all the usual diagnostic procedures required in severely ill patients, including endoscopy, liver biopsy, and even non-invasive imaging studies such as computed tomography or magnetic resonance. Up until now, there are no studies on HVPG in the pediatric population. The aim of this study is to report our experience with HVPG measurements in pediatric patients with portal hypertension due to advanced liver diseases.

Materials and methods

No financial support has been provided for this study. An informed consent to the single investigation was obtained in all cases, from a parent, after a full explanation of the purpose and nature of the procedure. The internal Institutional Research Review Board and Ethical Committee reviewed and approved the study.

This retrospective study was performed in 20 pediatric patients with chronic liver diseases, with patent portal vein, who were referred to the Interventional Radiology Department of a single transplant centre for the evaluation of portal hypertension in the period between October 2005 and December 2009. A review of the patients' charts, endoscopic studies, radiology imaging studies (computed tomography and/or magnetic resonance), HVPG measurements, and pathology reports was performed.

Eleven patients were female; the mean age was 82 ± 54 months (range 8–191 months) and the mean body weight was 24.2 ± 16.2 kg (range 5–61 kg). The cause of chronic liver disease was biliary atresia in nine patients, congenital hepatic fibrosis and autoimmune hepatitis in two, Wilson's disease, biliary cirrhosis due to choledocal cyst, cryptogenic chronic hepatitis, chronic hepatitis due to prolonged total parenteral nutrition, intra-hepatic chronic cholestasis, cystic fibrosis, and progressive familiar intra-hepatic cholestasis type 3 in one each. All patients with biliary atresia had undergone Kasai operation. Eleven patients had esophageal varices at endoscopy, 14 had perigastric and periesophageal collaterals at multi detector computed tomography or magnetic resonance imaging scan, three had ascites, 12 had low platelet count (<130.000 mm^3), and all had splenomegaly. Three patients had previous gastrointestinal bleeding. Individual clinical data and hemodynamic parameters of these patients are reported in Table 1.

Six patients underwent liver transplantation during the follow-up, three patients with biliary atresia, one with congenital hepatic fibrosis, one with progressive familiar intra-hepatic cholestasis type 3 and one with autoimmune hepatitis.

All the procedures were performed after an overnight fast, by two radiologists with 8 and 18 years, respectively, of experience in abdominal interventional radiology, in the angiographic suite (Advantx, General Electric Medical Systems, USA) under monitored anesthesia care with spontaneous respiration (Propofol intra-venous 125–300 mcg/kg/min) and local anesthesia, or under general anesthesia (Propofol intra-venous 125–300 mcg/kg/min and/or Sevofluorane 2.5% or 3%). Infusion of platelets and/or fresh frozen plasma were used in patients with severe coagulation defects (platelets <50.000 mm^3 and/or prothrombin activity <50%). In all patients the right internal jugular vein was punctured under ultrasound-guidance (Logic 7, General Electric Medical Systems, USA). In 16 patients a 7F vascular introducer (St. Jude Medical, Minnetonka, USA) was utilized, while in three patients below 10 kg of weight a 5F vascular introducer (St. Jude Medical, Minnetonka, USA) was used. The hepatic vein, right or middle, was catheterized under fluoroscopic guidance with a 5F Cobra 2 angiographic catheter (Angiodynamics, Queensbury, USA) and a hydrophilic wire (Terumo Europe, Leuven, Belgium). The hepatic venogram was performed by gentle hand injections of a small amount (2–6 cc) of iodixanol iso-osmolar contrast medium (Visipaque 320 mgI/ml, Amersham Health, Italy) with the catheter tip positioned in the mid/distal portion of the vein.

The angiographic catheter was then exchanged with a standard 5F occlusion balloon catheter (Boston Scientific, Cork, Ireland). A 4 mm diameter ultrathin balloon catheter (Smash peripheral balloon dilatation catheter, Boston Scientific, Cork, Ireland) was used in five patients, two with very thin hepatic veins and in the three patients below 10 kg of weight. Wedged (occluded) hepatic vein pressure (WHVP) and free hepatic vein pressure (FHVP) were obtained by inflating and releasing the balloon. The hepatic vein pressure gradient (HVPG) was estimated from the difference between WHPV and FHVP. All measurements were recorded using a pressure transducer set (Edwards Lifesciences, Unterscleissheim, Germay) linked to a multichannel recorder (Solar 8000, General Electric Medical Systems, USA) with a 30 mmHg scale capable of detecting small venous pressure changes. As currently performed in adult patients, HVPG measurements were performed with balloon catheters occluding a large hepatic vein branch measuring the WHVP of a large vascular territory, avoiding possible difference in values obtained when the catheter is wedged distally in different hepatic veins as a possible consequence of a heterogenic sinusoidal involvement by the disease affecting the liver [11]. Hemodynamic measurements were performed following established criteria [3]. According to these guidelines, the transducer was placed at the level of the midaxillary line (where the pressure transducer itself was calibrated at zero pressure); the value was considered accurate only when the recorded pressure was stable for at least 60 s; at least three different measurements were performed and the mean value was used for the study. Non-invasive monitoring of arterial pressure (automatic sphygmomanometer), heart rate (derived from the continuous EGC), and the oxygen saturation (pulse oximeter) were performed.

In four patients a transjugular liver biopsy, with a Quick-Core 18 Gauge needle biopsy system (Cook, William Cook Europe, Bjaeverskov, Denmark), was successfully performed after the HVPG measurement.

All patients had previous multi detector computed tomography and/or magnetic resonance imaging studies and the time interval between imaging studies and HVPG measurements was never longer than three months.

The data are reported as means ± standard deviation. Comparison between total procedural time and fluoroscopy time between patients with biliary atresia and patients without biliary atresia was done by paired *t* test using SPSS software (SPSS Institute Inc., Cary, NC). Statistical significance was established at $p < 0.05$.

Results

Hepatic vein catheterization was performed in all patients without complications. No complications linked to jugular vein puncture were observed. HVPG values were elevated in all but 3 patients, ranging between 2 and 33 mmHg (mean 11.3 ± 7.2 mmHg).

Unexpectedly, intra-hepatic venous–venous shunts (IVVS) were detected in 7 out of 9 patients with biliary atresia (Figs. 1–3) but in none of the patients with other types of chronic liver disease ($p = 0.01$). In four patients with biliary atresia and IVVS (Table 1: cases 2, 6, 7, 9) we were still able to adequately occlude a hepatic vein, distally to the IVVS, in a small hepatic parenchyma area in which the venogram did not show IVVS communication.

By contrast, in the other three patients with IVVS (Table 1: cases 3, 4, 5) despite the occlusion of a peripheral hepatic vein, a moderate IVVS was still visualized at the venogram; in these cases the HVPG underestimates portal pressure. Presently two patients had esophageal varices (one with previous bleeding) and one with large collaterals with a measured HVPG of 8 mmHg. By contrast, the HVPG in the remaining biliary atresia patients with varices and/or collaterals ranged between 15 and 33 mmHg, and was of 8 mmHg in one patient without varices, collaterals, or ascites, but with severe low platelets count. HVPG was 3 mmHg in the only biliary atresia patient without varices, collaterals, or ascites and with good platelet count. All but two non-biliary atresia patients had HVPG values $\geqslant$10 mmHg with either varices or collaterals or ascites, HVPG was 2 and 2.5mmHg in the only two non-biliary atresia patients without varices, collaterals, or ascites and with good platelet count.

The mean heart rate was 96 ± 15 beats/min (no significant differences between patients under beta-blocker therapy and without beta-blocker therapy), while mean arterial pressure was 56 ± 16 mmHg, data that is compatible with a hyperkinetic circulation. Interestingly all patients who had IVVS detected during hepatic vein catheterization had also these IVVS evaluated by imaging (Fig. 4).

The mean total time in the radiology suite was 55 min (range: 30–100 min); mean fluoroscopy time was 6.4 min (range: 2.5–15 min) including the fluoroscopy time for the transjugular liver