Published in final edited form as:

J Pediatr Gastroenterol Nutr. 2009 November ; 49(5): 607–612. doi:10.1097/MPG.0b013e3181a5267d.

Pulmonary Vascular Complications in Asymptomatic Children with Portal Hypertension

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Abstract

Objectives—To determine the prevalence of Portopulmonary Hypertension (PPHTN), Hepatopulmonary Syndrome (HPS), and Intrapulmonary Vascular Shunting (IPVS) in children with clinically stable portal hypertension and to assess the value of vasoactive peptide levels, biochemical tests and clinical signs or symptoms to predict these conditions.

Methods—A prospective, cross-sectional analysis was conducted on 33 children, ages 4 to 17 years, with stable cirrhosis (n=28) or extrahepatic portal hypertension (n=5). The children were screened for IPVS and hypoxia with contrast-enhanced echocardiography (cECHO) and pulse oximetry, and screened for pulmonary hypertension with Doppler echocardiography. Chemistries, x-rays, physical examinations and levels of vasoactive peptides were compared between subjects with IPVS and those with normal cECHO.

Results—No subject had pulmonary hypertension. Six (19%) had IPVS, all of which had intrahepatic causes of portal hypertension, and one of whom had HPS. Compared to subjects with normal cECHO, those with IPVS had biochemical evidence of more advanced liver disease and higher b-type natriuretic peptide (BNP) levels.

Conclusions—PPHTN and HPS appear to be rare in clinically stable children with portal hypertension. IPVS was present in 19% of these patients. A novel finding of this study is the elevation of BNP in children with IPVS.

Keywords

Intrapulmonary; shunting; BNP; natriuretic; endothelin

INTRODUCTION

Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (PPHTN) are distinct pulmonary vascular complications of hepatic and extrahepatic portal hypertension (1). HPS is defined as dilated pulmonary capillaries and precapillary arteriovenous malformations resulting in intrapulmonary vascular shunting (IPVS), ventilation-perfusion mismatching and

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None of the authors have any potential, perceived, or real conflict of interest to disclose.

chronic hypoxemia in the setting of liver disease or portal hypertension (2). PPHTN is defined as pulmonary artery hypertension with an elevated mean pulmonary artery pressure and increased pulmonary vascular resistance caused by a pulmonary arteriopathy in the setting of portal hypertension and in the absence of underlying cardiopulmonary disease (2,3). PPHTN and HPS are estimated to occur in 2–10% and 4–29%, respectively, of adults with cirrhosis (1). Both PPHTN and HPS are associated with increased morbidity and mortality and are significant risk factors for orthotopic liver transplantation (OLT). However, resolution of both disorders is possible after successful OLT (4–7). PPHTN and HPS have been reported in children with portal hypertension from both cirrhosis and from congenital or acquired portal vein abnormalities, however, the incidence of these complications in children is unknown (8–10).

PPHTN and HPS have been diagnosed in children after the onset of cardiopulmonary symptoms or during OLT evaluation for end-stage liver disease. Following our experience of identifying advanced pulmonary hypertension in seven children who presented with symptomatic PPHTN (8), we hypothesized that children without cardiopulmonary symptoms and with stable portal hypertension might have milder forms of PPHTN or HPS that could be detected by screening and might be amenable to intervention. To test this hypothesis, we conducted a prospective study to evaluate the prevalence and predictors of PPHTN and HPS in clinically stable pediatric patients with portal hypertension.

PATIENTS AND METHODS

Subjects

Thirty-three children with portal hypertension and no obvious cardiopulmonary symptoms were evaluated in a prospective, cross-sectional study. Subjects were identified by a review of patient records at the Pediatric Liver Center at The Children's Hospital. All subjects had a prior diagnosis of portal hypertension defined by either: a) clinical evidence of esophageal or gastric varices, portal hypertensive gastropathy, splenomegaly, thrombocytopenia, or cirrhosis, b) histologic evidence of cirrhosis, or c) radiologic evidence of portal vein thrombosis, cavernous transformation of the portal vein, splenomegaly or obstructed hepatic venous flow. Patients were excluded if they had a prior diagnosis of PPHTN, HPS, primary lung disease, decompensated heart disease, chronic lung disease of prematurity, or were being evaluated for or had undergone OLT. The Colorado Multiple Institutional Review Board and the Scientific Advisory Committee of the Pediatric Clinical Translational Research Center (CTRC) approved the study protocol and written informed consent and assent were obtained from the parents and participants.

Data obtained from subjects' records included age, gender, underlying diagnoses, causes of portal hypertension, prior complications and management of portal hypertension. Subjects were admitted to the pediatric CTRC and interviewed for symptoms of liver disease or cardiopulmonary complications. Physical examinations and anthropometric measurements were performed to evaluate for clinical evidence of portal hypertension, chronic liver disease and to assess growth. Complete blood counts, chemistry tests, and coagulation studies were obtained. Child-Pugh scores were calculated. Doppler ultrasonography was performed to assess hepatic arterial flow and hepatic venous flow, portal and splenic vein flow, presence of varices, ascites, hepatosplenomegaly and abdominal situs.

Evaluation for PPHTN

Doppler echocardiography was used to detect and measure tricuspid regurgitant velocity (TR) and to evaluate for right ventricular hypertrophy (RVH) and interventricular septal flattening. TR and estimated right atrial pressure (RAP) were used to calculate the pulmonary artery

systolic pressure (PASP) using the modified Bernoulli equation ($\text{PASP (mmHg)} = 4 \times \text{TR}^2 \text{ (m/sec)} + \text{RAP (mmHg)}$). PPHTN was defined as a $\text{PASP} \geq 40 \text{ mmHg}$ with interventricular wall flattening or RVH. Chest x-rays and electrocardiograms were performed to evaluate for cardiomegaly, enlarged pulmonary arteries, and right heart enlargement.

Evaluation for HPS and IPVS

Contrast echocardiograms (cECHO) were performed to screen for IPVS. 3–5 ml of agitated saline was injected into a peripheral, intravenous catheter and echocardiography was performed. IPVS was defined as microbubbles entering the left atrium within 3 to 6 cardiac cycles after entering the right heart. HPS was diagnosed when IPVS was associated with hypoxemia. Hypoxemia was defined as mean oxygen saturation (SaO_2) $\leq 92\%$ determined by pulse oximetry over ten minutes. Orthodeoxia, a common finding in HPS, was defined as a decrease in SaO_2 by 6 or more percentage points or to a value $\leq 92\%$ upon standing from a supine position.

Assays for Vasoactive-Peptides

A panel of vasoactive peptides was measured from fasting plasma samples in the Pediatric CTRC core laboratory including endothelin-1, nitrate and nitrites, cyclic AMP, cyclic GMP, and 6-keto-PGF1 α . Assays used and reference ranges are as follows: endothelin-1 (R&D Systems Quantitative Enzyme Immunoassay technique, 0.3–0.9 pg/mL); nitrate and nitrites (R&D Systems Parameter Total NO/Nitrite/Nitrate Kit, Nitrates 32–80 $\mu\text{mole/L}$, Nitrites 63–165 $\mu\text{mole/L}$); cyclic AMP (R&D Systems Parameter competitive binding technique, 32–194 pmole/mL), cyclic GMP (R&D Systems Parameter competitive binding technique, 75–219 pmole/mL), and 6-keto-PGF1 α (Cayman Chemicals Competitive Enzyme Immunoassay, no reference range given). Measurement of BNP was performed at Mayo Medical Laboratories using a Triage® BNP Test for Beckman Coulter Immunoassay Systems (0–64 pg/ml) (11).

Statistical Analysis

The significance of categorical variables was determined by Fisher's exact test. Continuous variables were compared by a two sample Wilcoxon rank sum test. Differences were considered significant for $P < 0.05$.

RESULTS

Baseline Characteristics of Patients

Thirty-three children, ages 4 to 17 years (median 10 years), with portal hypertension were identified (Table 1). The underlying cause of portal hypertension included biliary atresia in 19, cavernous transformation of the portal vein in 5, autoimmune hepatitis in 4, congenital hepatic fibrosis in 3, one with hepatic fibrosis associated with 6-thioguanine therapy for leukemia and one with cryptogenic cirrhosis. All patients lived at an elevation of at least 1,600 meters above sea level.

Portopulmonary Hypertension

PPHTN was not diagnosed in any of the 33 subjects. The median PASP on 9 subjects with detectable tricuspid regurgitation was 25 mmHg, (range 16–37 mmHg). One subject with biliary atresia and polysplenia had RVH on echocardiogram and electrocardiogram that was associated with previously undiagnosed cardiac heterotaxy syndrome. No other subject had RVH or septal wall flattening. Eight had abnormal chest x-rays with mild prominence of central pulmonary arteries or mild cardiomegaly; however, all 8 had normal cardiac ECHOs.

Intrapulmonary Vascular Shunting and Hepatopulmonary Syndrome

Eight of the 33 subjects had abnormal cECHO (Table 1). Two subjects had a small patent foramen ovale, thus, IPVS could not be determined. Six of the remaining 31 subjects (19%) had IPVS (95% confidence interval 7% to 37%). Two subjects with IPVS had a trend toward orthodeoxia with their SaO₂ decreasing 3.8 and 5.1 percentage points each after standing from supine position. One of these two subjects had hypoxia with a mean SaO₂ of 92% supine and 90% standing, thus, was the only subject to meet criteria for HPS.

Characteristics of Subjects with IPVS

The six subjects with IPVS had intra-hepatic causes of portal hypertension, including four with biliary atresia, one congenital hepatic fibrosis and one cryptogenic cirrhosis (Table 2). IPVS subjects were 4 to 14 years old (median 8 years) and five were female. Compared to the 25 subjects with normal cECHO, those with IPVS had similar frequency of previous esophageal varices, gastrointestinal bleeding, ascites or hypersplenism. A similar percentage of subjects with and without IPVS reported dyspnea on exertion, cough, fatigue, syncope, dizziness, abdominal pain, bruising, epistaxis and pruritus, however, subjective weakness was more frequent in those with IPVS (3 of 6) compared to subjects with normal cECHO (2 of 25), ($P = 0.038$). Weight, height and body mass index z-scores were not significantly different between the two groups. Subjects with IPVS had lower albumin and higher direct bilirubin, GGT, AST, ALT, and NH₃, and trended toward higher Child-Pugh scores (3 of the 6 having a Child Pugh Score B compared with 4 of 25 without IPVS, $p=0.11$). Oxygen saturations were similar in the two groups: median SaO₂ with IPVS was 97.6% supine and 96.7% standing, compared to 97.2% supine and 97.4% standing in those with normal cECHO (Table 3). Chest x-rays were more likely to detect prominent central pulmonary arteries or mild cardiomegaly in subjects with IPVS (Table 3).

Vasoactive-Peptide Levels

Cyclic GMP was lower and BNP was higher in subjects with IPVS compared to those with normal cECHO (Table 4). Otherwise, no differences were observed in the levels of potential vasoactive peptides among these groups.

DISCUSSION

In this prospective evaluation of 33 clinically stable children with portal hypertension, PPHTN was not observed, IPVS was present in 19% and HPS was diagnosed in one subject. IPVS was associated with lower serum albumin, higher aminotransferases and higher ammonia levels suggesting more advanced liver disease and portal hypertension in these patients. A novel finding of this study was the elevated BNP in patients with IPVS, which may be a correlate of the reported increased left atrium volume in patients with IPVS (12).

The pathogenesis of PPHTN and HPS remains unknown. Proposed theories suggest these disorders result from a combination of hyperdynamic circulation, increased cardiac output, sheer injury to vascular walls and an imbalance of circulating vasoactive peptides (13,14). Abnormal hepatic synthesis of vasoactive peptides, such as endothelin-1, or impaired hepatic metabolism of intestinally derived endotoxins, cytokines and neurohormones may result in these substances reaching the pulmonary vascular bed via portosystemic shunting, directly altering vessel tone or leading to pulmonary vascular inflammation and remodeling. The resulting pathology is strikingly different in these two disorders with vasodilation of pulmonary arterioles and capillaries causing arteriovenous shunting in HPS and intimal fibrosis with endothelial and smooth muscle cell proliferation leading to increased pulmonary vascular resistance in PPHTN (1). The proposed pathogenesis, symptoms and prognosis of both disorders have been summarized in detail in recent reviews (1,4,15). The nitric oxide cGMP

pathway is considered to play a key role in the pathogenesis of HPS, however, this finding remains controversial as not all studies have demonstrated an increase in cGMP or nitric oxide metabolites. In our study, circulating measures of the NO-cGMP cascade were not increased, but rather decreased, in the IPVS patients. A recent study reported that left atrial volume is a novel predictor of hepatopulmonary syndrome (12). In accordance with these findings we found that BNP was elevated in those children with IPVS.

HPS has been reported in children with liver disease, cirrhosis, hepatic venous outflow obstruction and with congenital or acquired extrahepatic portal vein abnormalities (9,16–21). The absence of liver disease in some adults and children with HPS supports the hypothesis that the portal hypertension or porto-systemic shunting is the key factor in the development of this disorder. We included five subjects with extrahepatic portal vein thrombosis and portal hypertension in this study, however, none had IPVS or hypoxia. Larger numbers of these patients will need to be studied to determine the frequency and full extent of pulmonary vascular complications in extrahepatic causes of portal hypertension.

Little is known regarding the prevalence and progression of PPHTN, HPS or IPVS in children with liver disease or portal hypertension. A recent preliminary report described the presence of IPVS in 17 (32%) of 52 children with cirrhosis and evidence of hepatic failure (22). Nine subjects (16%) with IPVS had HPS ($\text{PaO}_2 < 70$ mmHg). The higher rates of both IPVS and HPS in this study compared to our study suggest that advanced liver disease increases the frequency of these pulmonary complications in children. This is consistent with studies in adults in which the risk of HPS appears to be highest in Child C patients (1).

A retrospective study of 26 children with IPVS reported progression of hypoxemia in all ten children who had repeat PaO_2 measurements and progression of IPVS in the 5 who had repeat pulmonary scintiscans (9). This progression was often rapid, occurring within 12 months. In contrast, hypoxemia in HPS may improve following OLT (23). It remains unclear whether the progression of IPVS is dependent on the duration or the severity of liver disease and portal hypertension. Early recognition of HPS and monitoring progression of IPVS and hypoxemia may be important in the timing of OLT evaluations.

In order to avoid obtaining arterial blood gas measurements for our study because of ethical concerns, we screened for hypoxia using pulse oximetry. We defined hypoxia as $\text{SaO}_2 \leq 92\%$ at the Denver elevation of 1,600 m and orthodeoxia as a decrease in SaO_2 by 6 percentage points upon standing. One of the six children with IPVS had hypoxia by these criteria. Previous consideration for the utility of pulse oximetry to detect arterial hypoxemia found that SaO_2 may overestimate the PaO_2 , but, that as a screening tool a $\text{SaO}_2 \leq 94\%$ would detect all patients with a $\text{PaO}_2 < 60$ mmHg (24). Therefore, it is possible that we would have diagnosed additional subjects with HPS had we measured PaO_2 from arterial blood gases. However, because of its noninvasive nature, we believe that SaO_2 by pulse oximetry is an appropriate alternative to arterial blood gas measurements to screen stable children with portal hypertension or cirrhosis. Furthermore, our study demonstrated that serum BNP may be a biomarker for the presence of IPVS, however, further evaluation using a larger patient population will be required to confirm this observation.

Most patients with PPHTN are asymptomatic, thus, routine screening of adults undergoing evaluation with Doppler ECHO for OLT has been recommended (25). Patients with elevated PASP by ECHO should undergo confirmatory right heart catheterization (26,27). Systemic hypertension, a loud pulmonary component of the second heart sound, RVH, and right ventricular dilation or heave are clinical findings associated with PPHTN in some adults (1). In our earlier series of 7 children with PPHTN, common findings included a prominent pulmonary artery on chest x-ray, RVH on EKG, heart murmur or a history of syncope (8). In

the current study of 33 children with stable portal hypertension, three had a history of syncope, nine had heart murmurs, five had a prominent pulmonary artery on chest x-ray, and one had RVH by EKG, yet none had pulmonary hypertension by Doppler ECHO. Thus, clinical signs and symptoms cannot be relied upon to identify patients with PPHTN. Our findings also suggest that the levels of vasoactive peptides measured in this study do not predict the presence of PPHTN.

In conclusion, PPHTN appears to be rare in clinically stable pediatric patients with portal hypertension. IPVS was present in 19% of these patients who resided at elevation above 1,600 m, although HPS was rare. Although our study does not support the need to extensively screen for PPHTN or HPS in all clinically stable children with cirrhosis or portal hypertension, we suggest that pulse oximetry be performed during routine exams. Further evaluation with Doppler ECHO, cECHO, EKGs and chest x-rays should be reserved for patients with suggestive clinical symptoms, particularly cardiac murmurs, syncope and shortness of breath, hypoxia or orthodeoxia on pulse oximetry, and perhaps at the time of OLT evaluation. The rate of progression of IPVS to HPS, the utility of BNP as a predictor of IPVS and the timing of OLT evaluation in children with IPVS will need to be determined in prospective studies.

Acknowledgments

Financial Support:

Support: MO1-RR00069, General Clinical Research Centers Program, NCRR, NIH Provided funding for study costs, including tests and data analysis.

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Table 1**Screening for Portopulmonary Hypertension and Hepatopulmonary Syndrome in Asymptomatic Children**

33 Children with Portal Hypertension	
Age 4yr – 17yr (median 10 yr.), 20 female	
Diagnoses: 19 Biliary atresia (2 polysplenia syndrome)	
5	Portal vein thrombosis & cavernous transformation of the portal vein (CTPV)
4	Autoimmune hepatitis (AIH)
3	Congenital hepatic fibrosis (CHF)
1	6-Thioguanine associated hepatic fibrosis
1	Cryptogenic Cirrhosis
0 / 33 Portopulmonary Hypertension	
1 / 33 Hepatopulmonary Syndrome	
8 / 33 Abnormal contrast echocardiograms	
2 / 33 Patent foramen ovale (IPVS indistinguishable)	
Age 17yr (n=2)	
Diagnoses: AIH, CTPV	
6 / 31 (19%) Intrapulmonary Vascular Shunting (IPVS)	
Age 4yr – 14yr (median 8 yr), 5 female	
Diagnoses: BA (n=4), CHF (n=1), Cryptogenic cirrhosis (n=1)	
Hypoxia: 1 / 31	

Table 2

Comparison of Patients with Intrapulmonary Vascular Shunting (IPVS) vs. Normal Contrast Echocardiograms (cECHO)

	Normal cECHO	IPVS	
Etiology of Portal Hypertension	(n=25)	(n=6)	
Intrahepatic	21	6	
Extrahepatic	4	0	
Complications of Portal Hypertension			
Esophageal varices/ GI Bleeds	10	2	
Ascites	2	1	
Thrombocytopenia	13	4	
Symptoms & Signs			
Dyspnea with exertion	11	1	
Fatigue	10	3	
Subjective weakness	2	3	(P=0.038)
Syncope	1	2	
Abdominal pain	11	1	
Spider telangiectasias	11	4	
Palmar erythema	3	2	
Cardiac murmur	6	2	
Weight (median z-score)	0.31	0.04	
Height (median z-score)	-0.14	-0.31	
BMI (median z-score)	0.66	0.77	
Childs-Pugh Score			
A	21	3	
B	4	3	
C	0	0	
Laboratory Tests (median values)			
Albumin (g/dL)	3.7	3.2	(P=0.012)
Total Bilirubin (mg/dL)	0.5	0.8	(P=0.086)
Direct Bilirubin (mg/dL)	0.2	0.4	(P=0.026)
Alkaline phosphatase (IU/L)	306	459	(P=0.077)
GGT (IU/L)	33	147	(P=0.030)
AST (IU/L)	34	89	(P=0.045)
ALT (IU/L)	45	97	(P=0.036)
NH ₃ (μmol/L)	31	67	(P=0.011)
WBC (10 ³ /uL)	3.4	3.6	(P=0.855)
Platelet Count (10 ³ /uL)	104	100	(P=0.910)

Table 3

Cardiopulmonary Evaluation of Patients with Intrapulmonary Vascular Shunting (IPVS) vs. Normal Contrast Echocardiograms (cECHO)

	Normal cECHO	IPVS
SaO₂	(n=25)	(n=6)
Supine (median)	97.2%	97.6%
Standing (median)	97.4%	96.7%
Hypoxia	0	1 [*]
Orthodeoxia	0	2 [†]
Cardiac Evaluation		
EKG Abnormal	1 ^{**}	0
CXR Abnormal	4 [#]	4 ^{##}
		(P=0.029)

* Mean SaO₂ 92.8% supine, 90.4% standing

† SaO₂ 98.1% supine → 93% standing and SaO₂ 92.8% supine → 89% standing

** Right ventricular hypertrophy

Prominent central pulmonary vessels (3), mild cardiomegaly (1)

Prominent central pulmonary vessels (2), mild cardiomegaly (2)

Table 4

Vasoactive-Peptide Levels of Patients with Intrapulmonary Vascular Shunting (IPVS) vs. Normal Contrast Echocardiograms (cECHO), Median Values (Range)

	Normal cECHO	IPVS	P Value
Peptide	(n=25)	(n=6)	
Nitrates (NO ₂) (umole/L)	48 (41–112)	88.5 (38–113)	0.11
Nitrites (NO ₃) (umole/L)	37 (18–87)	44 (24–141)	0.55
Cyclic AMP (pmole/mL)	59 (30–241)	54 (34–73)	0.31
Cyclic GMP (pmole/mL)	161 (120–239)	131 (120–184)	0.03
6-keto-PGF-1a (pg/mL)	595 (294–1910)	613 (312–1717)	0.88
Endothelin-1 (pg/mL)	1.2 (0.8–5.5)	1.8 (1.1–2.0)	0.16
B-Type Natriuretic Peptide (pg/mL)	17 (5–127)	59 (15–177)	0.02