Liver and Systemic Hemodynamics in Children With Cirrhosis: Impact on the Surgical Management in Pediatric Living Donor Liver Transplantation

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Cirrhosis in adults is associated with modifications of systemic and liver hemodynamics, whereas little is known about the pediatric population. The aim of this work was to investigate whether alterations of hepatic and systemic hemodynamics were correlated with cirrhosis severity in children. The impact of hemodynamic findings on surgical management in pediatric living donor liver transplantation (LT) was evaluated. Liver and systemic hemodynamics were studied prospectively in 52 children (median age, 1 year; 33 with biliary atresia [BA]). The hemodynamics of native liver were studied preoperatively by Doppler ultrasound and intraoperatively using invasive flowmetry. Portosystemic gradient was invasively measured. Systemic hemodynamics were studied preoperatively by Doppler transthoracic echocardiography and intraoperatively by using transpulmonary thermodilution. Hemodynamic parameters were correlated with Pediatric End-Stage Liver Disease (PELD) score and the histological degree of fibrosis (collagen proportionate area [CPA]). Cirrhosis was associated with a 60% reduction of pretransplant total liver flow (n = 46; median, 36 mL/minute/100 g of liver) compared with noncirrhotic livers (n = 6; median, 86 mL/minute/100 g; $P = 0.002$). Total blood flow into the native liver was negatively correlated with PELD ($P < 0.001$) and liver CPA ($P = 0.005$). Median portosystemic gradient was 14.5 mm Hg in children with cirrhosis and positively correlated with PELD ($P < 0.001$). Portal vein (PV) hypoplasia was observed mainly in children with BA ($P = 0.02$). Systemic hemodynamics were not altered in our children with cirrhosis. Twenty-one children met the intraoperative criteria for PV reconstruction using a portoplasty technique during the LT procedure and had a smaller PV diameter at pretransplant Doppler ultrasound (median = 3.4 mm; $P < 0.001$). Cirrhosis in children appears also as a hemodynamic disease of the liver, correlated with cirrhosis severity. Surgical technique for PV reconstruction during LT was adapted accordingly.

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In adults, portal hypertension and cirrhosis are associated with hemodynamic changes in hepatic and systemic circulation.[1] However, knowledge regarding the corresponding hemodynamic alterations in children with cirrhosis is limited.[2,3] Biliary atresia (BA) is characterized by inflammation and fibrosis of intrahepatic and extrahepatic biliary tracts that leads to biliary cirrhosis.[4] BA constitutes the first indication for liver transplantation (LT) in the pediatric population, representing at least 50% of all cases in most series.[5,6] Several authors have reported that cirrhosis secondary to BA may be associated with portal vein (PV) hypoplasia (defined as an internal PV diameter ≤ 4 mm at pretransplant Doppler ultrasound)[7] and severe alterations of liver hemodynamic parameters.[8-10] PV hypoplasia may lead to technical difficulties in PV reconstruction during LT, which increases the risk of

Abbreviations: ARI, arterial resistance index; BA, biliary atresia; CI, confidence interval; CPA, collagen proportionate area; HA, hepatic artery; HABR, hepatic artery buffer response; LT, liver transplantation; NS, not significant; PELD, Pediatric End-Stage Liver Disease; PV, portal vein; PVP-CVP, portal vein pressure–central venous pressure gradient.

posttransplant PV complications, and thus the risk of graft loss.[11-13] Our group previously reported that the laterolateral portoplasty technique for PV reconstruction during LT in patients with PV hypoplasia could alleviate the increased risk of post-LT PV thrombosis.[14]

A prospective single-center study was conducted to invasively assess native liver and systemic hemodynamics in children with cirrhosis at the time of LT. Moreover, correlation between invasive and noninvasive measurements was also performed. We hypothesized that abnormal pretransplant liver and systemic hemodynamics, and PV hypoplasia (characterized by histological changes in the extrahepatic and intrahepatic PV), may be correlated with cirrhosis severity. We also hypothesized that native liver hemodynamic parameters may help to predict the need to use a portoplasty technique for PV reconstruction during the LT procedure.

Patients and Methods

PATIENTS

The prospective observational study included 52 pediatric patients (<18 years) who received a primary LT from a living related donor (segments 2-3 for 46 children; segments 2-3-4 for 6 children) at Cliniques Universitaires St. Luc, Brussels, Belgium, between March 2012 and October 2014. The study was approved by the hospital ethics committee (protocol number: 2010/23DEC/407; approval number: B403201110642), and written informed consent was provided by the parents (and adolescent children). Patients with preexisting pulmonary or hepatopulmonary syndrome or cardiac disease were excluded from the study. Pediatric End-Stage Liver Disease (PELD) score was calculated at pretransplant assessment by computing the total bilirubin, albumin, international normalized ratio, age, and growth retardation.[15]

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NATIVE LIVER HEMODYNAMICS: NONINVASIVE PRETRANSPLANT ASSESSMENT

Within 15 days before transplant, all children were placed in the supine position after a 6-hour fast and a detailed Doppler ultrasound of the native liver was done by 1 of 3 experienced pediatric radiologists. Internal PV diameter, portal flow direction (hepatopetal, fluctuant or absent, or hepatofugal), PV velocity, and mean hepatic artery (HA) velocity were recorded. PV flow was computed according to the following formula: PV velocity $\times$ ($\pi \times$ [internal PV diameter/2]^2. Hepatic arterial resistance index (ARI) was calculated as (maximal systolic velocity – minimal diastolic velocity)/maximal systolic velocity, and was considered abnormal when $\geq$1. All Doppler measurements were performed 3 times using a 9-4 MHz convex transducer and a 12-5 MHz linear transducer (Philips iU22, Philips Medical System, Eindhoven, the Netherlands), and the mean values were reported. According to the literature, PV hypoplasia was defined as an internal PV diameter $\leq$ 4 mm, regardless of patient age.[16-18]

SYSTEMIC HEMODYNAMICS: NONINVASIVE PRETRANSPLANT ASSESSMENT

On the same day as liver Doppler ultrasound, mean systemic arterial pressure, heart rate, and respiratory rate were recorded. Cardiac output and left ventricular ejection fraction were measured using Doppler transthoracic echocardiography performed by 1 of 2 pediatric cardiologists with S8-3 MHz and S5-1 MHz sector transducers (Philips iE33, Philips Medical System, Eindhoven, the Netherlands). Body weight and body surface were determined to calculate cardiac index.

INTRAOPERATIVE ASSESSMENT OF NATIVE LIVER HEMODYNAMICS USING INVASIVE METHODS

At the time of dissection of the native liver and immediately before HA ligation, the external diameter of the

recipient's vessels was accurately measured, and average PV and HA flows were recorded in hemodynamically stable patients using an ultrasound transit time flowmeter (Butterfly Flowmeter, Medi Stim ASA Medical, Oslo, Norway), this method being previously validated in patients undergoing vascular surgery as in patients requiring LT.[19,20] To measure PV pressure, a needle was inserted into the native PV and connected to a pressure line. Central venous pressure was concomitantly measured, and the portal vein pressure–central venous pressure gradient (PVP-CVP) was calculated. The native liver was weighed immediately after the hepatectomy. Perfusion rates are expressed in mL/minute/100 g of the liver. The same surgeon performed all measurements.

INTRAOPERATIVE CARDIOPULMONARY MONITORING

We used transpulmonary thermodilution (PiCCO), this technique being considered as the gold standard technique for the measurement of pediatric cardiac output.[21,22] A central venous catheter (arrow 4-Fr or 5-Fr, double or triple lumen) was inserted into the left or right subclavian vein and an arterial catheter with a thermistor was inserted into a femoral artery (3-Fr PV2013L07 if ≤ 20 kg; and 4-Fr PV2014L08 if > 20 kg) under ultrasound guidance. The 2 catheters were connected to a PiCCO plus device (version 5.2.2, Pulsion Medical Systems AG, Munich, Germany). A predetermined volume of cold saline solution (5 mL if ≤ 20 kg, or 10 mL if > 20 kg, at a temperature of <8 °C) was injected via the distal port of the central venous catheter. The cold saline dissipation curve measured at the site of the arterial catheter was used to calculate the cardiac index (Stewart-Hamilton principle). Each measurement was repeated 3 times to determine the mean cardiac index. PiCCO was used in the first 28 patients (19 BA, 7 non-BA patients with cirrhosis, and 2 without cirrhosis). Because 4 of them developed femoral artery thrombosis (successfully treated with intravenous fraxiparine), invasive cardiac output measurements were no longer performed in the remaining patients included in the study.

SURGICAL TECHNIQUES

Donor surgery and LT were performed as previously described.[14,23,24] In the recipient, PV was dissected proximally and distally to obtain sufficient length, and this dissection was extended downward to the confluence of superior mesenteric and splenic veins, including the ligature of the coronary vein in case of PV hypoplasia. The surgical technique used for PV anastomosis was an end-to-end truncular anastomosis without a vein graft, with 7/0 absorbable monofilament running sutures, this technique being performed in the absence of stenosis or sclerosis of the recipient's PV (used in 31/52 children). Alternatively, a portoplasty technique using a patch of the donor's inferior mesenteric vein was performed in the remaining 21 children in whom recipient's PV was of insufficient external diameter (intraoperative measure ≤ 5 mm) and/or with sclerotic wall appearance, as previously described.[14] Patency of vascular anastomoses was assessed intraoperatively by using Doppler ultrasound with a 7.5 MHz convex transducer (Aloka IPF-1503, Aloka, Tokyo, Japan).

HISTOLOGICAL STUDIES ON NATIVE LIVERS AND PVS

A wedge of native liver and a portion of native extrahepatic PV were formalin-fixed for histological analysis. An experienced liver pathologist, who was blinded to the clinical data, evaluated liver fibrosis in tissues stained with Masson's trichrome using a METAVIR equivalent score for fibrosis (0 to 4), and the Laennec score (4A, 4B, 4C) in case of cirrhosis.[25] Cirrhosis was defined as a METAVIR score of 4. Sirius red staining was performed to quantify liver fibrosis. Mean collagen proportionate area (CPA) was measured using Axiovision software (Zeiss, Oberkochen, Germany) on 10 images/sample ($\times 5$ original magnification) acquired on an Axioskop40 microscope (Zeiss). According to the work of Tsochatzis et al. in 2014, cirrhosis can be accurately subclassified using quantification of fibrosis with CPA.[26]

The surfaces of intrahepatic HA and PV lumens were measured in 3-5 large portal tract vessels in hematoxylin-eosin–stained sections using Tissue IA software (Leica Biosystems, Dublin, Ireland) after digitalization with a SCN400 slide scanner (Leica Biosystems, Wetzlar, Germany).

Alpha-actin smooth muscle immunostaining was performed on the native extrahepatic PV (obtained perpendicular to its main axis), and the intima/total wall thickness ratio was measured in the thickest part of the vein wall. Images (5 fields of view per sample) were acquired using an Axioskop40 microscope (Zeiss) with a $\times 10$ objective and analyzed using Axiovision software. The same author performed all measurements.

TABLE 1. Demographic Data of the 52 Pediatric Patients (<18 Years) Who Received a Primary LT from a Living Related Donor at Cliniques Universitaires St. Luc, Brussels, Belgium, Between March 2012 and October 2014

	Patients With Cirrhosis Without BA (n = 13)	Patients With Cirrhosis With BA (n = 33)	Patients Without Cirrhosis (n = 6)
Age, years	5.6 (2.5-8.8)	0.8 (0.7-1.0)	2.3 (1.4-3.5)
PELD	13.4 (3.8-22.6)	21.7 (18.3-25.6)	0 (0.0-5.1)
Body weight, kg	18.1 (11.1-25.0)	7.8 (7.4-8.3)	11.5 (7.9-14.5)
Diagnosis	Metabolic disease (n = 3) Alagille syndrome (n = 2) Progressive familial intrahepatic cholestasis (n = 2) Cirrhosis of unknown etiology (n = 2) Autoimmune hepatitis (n = 2) Primary sclerosing cholangitis (n = 1) Nonsyndromic bile duct paucity (n = 1)	BA (n = 33)	Liver malignancy (n = 5) Alagille syndrome (n = 1)
Native liver weight, g	589 (442-655)	468 (419-486)	503 (301-568)
Liver graft weight, g	309 (266-336)	283 (262-295)	279 (213-344)
Native liver weight/body weight, %	3.9 (2.7-4.3)	5.9 (5.4-6.1)	4.1 (3.2-4.9)
Liver graft weight/body weight, %	1.9 (1.4-2.3)	3.6 (3.3-3.8)	2.6 (2.0-2.8)
Liver graft weight/native liver weight, %	55.7 (44.2-72.1)	62.9 (54.7-70.2)	62.9 (36.3-83.0)
Total graft ischemic time, minutes	181 (156-199)	184 (176-193)	171 (138-204)

NOTE: Values expressed as median (95% CI).

STATISTICAL ANALYSIS

Continuous or ordered variables are expressed as median values, with 95% Hodges-Lehmann confidence intervals (CIs). For comparison of 2 percentages, we used the Nurminen and Mutanen exact test, which is convenient for small values.[27] To compare more than 2 categorical variables, we used the chi-square test. For comparison of ordered variables, we used the Smirnov test. For comparison of continuous variables, we used the Wilcoxon rank test (paired or unpaired), as needed. For group comparisons, we used rank contrasts according to Akritas et al.[28] For correlations, we used Kendall's tau rank test. For the measure of intrahepatic HA and PV lumens, we used means inversely pondered to the variances (± standard error of the means) instead of rank tests because there were multiple values, compatible with a normal distribution. All tests were 2-tailed, and a P value < 0.05 was considered significant. Statistical analyses were performed using SPSS software package, version 22 for MAC (SPSS Inc., Chicago, IL).

Results

STUDY POPULATION

The median age at transplantation was 1 year (95% CI, 0.5-14 years). The pretransplant diagnoses were BA (n = 33, 63.5%; including 3 children with BA splenic malformation syndrome), liver malignancy (n = 5, 9.6%), Alagille syndrome without cardiac function anomalies (n = 3, 5.8%), metabolic diseases (n = 3, 5.8%), progressive familial intrahepatic cholestasis (n = 2, 3.8%), cirrhosis of unknown etiology (n = 2, 3.8%), auto-immune hepatitis (n = 2, 3.8%), primary sclerosing cholangitis (n = 1, 1.9%), and nonsyndromic bile duct paucity (n = 1, 1.9%). In this study population, 46 children had cirrhosis (33 BA, 13 non-BA), whereas 6 patients did not have cirrhosis (including 5 liver malignancies and 1 Alagille syndrome). The demographic data of these 3 subgroups (children with cirrhosis with and without BA, and patients without cirrhosis) are given in Table 1.

Regarding the post-LT outcomes, during the minimal 6-month follow-up period, 1 patient (1.9%) died from a massive gastrointestinal hemorrhage 1 month after the first LT, and 10 days after retransplantation for PV thrombosis. One patient (1.9%) had HA thrombosis, 4 (7.7%) had PV thrombosis (3 BA with pre-LT PV hypoplasia at Doppler ultrasound; 1 of them with BA splenic malformation syndrome), and 6 (11.5%) had biliary complications. No patient had posttransplant Budd-Chiari syndrome.

NATIVE LIVER AND SYSTEMIC HEMODYNAMICS: NONINVASIVE PRETRANSPLANT ASSESSMENT

At pre-LT Doppler ultrasound of the native liver, children with cirrhosis had a smaller extrahepatic internal

TABLE 2. Noninvasive Native Liver Hemodynamic Parameters According to the Pretransplant Diagnosis in a Population of 52 Pediatric Patients Undergoing a Primary LT From a Living Related Donor at Cliniques Universitaires St. Luc, Brussels, Belgium, Between March 2012 and October 2014

Native Liver Doppler Ultrasound Hemodynamic Parameter	Patients With Cirrhosis Without BA (n = 13)	Patients With Cirrhosis With BA (n = 33)	*P* Value*	Children Without Cirrhosis (n = 6)
Internal PV diameter, mm	6.4 (4.6-8.7)	3.8 (3.4-4.2)	0.001	5.9 (4.0-6.7)
PV hypoplasia, %	4/13 (31%)	21/33 (64%)	0.02	0/6 (0%)
Pathologic PV flow, %	4/13 (31%)	19/33 (58%)	0.25 (NS)	0/6 (0%)
PV velocity, cm/seconds	23.5 (16.0-30.5)	12.5 (3-16)	0.005	28.5 (18-51)
PV flow, mL/minute	261 (122-382)	78 (51-105)	0.002	230 (91-321)
Mean HA velocity, cm/seconds	46 (36-63)	55 (47.5-63.0)	0.27 (NS)	41 (21-79)
Hepatic ARI	0.8 (0.7-0.9)	0.9 (0.9-1.0)	0.004	0.7 (0.6-0.8)

NOTE: Native liver hemodynamic parameters are collected by Doppler ultrasound within 15 days before transplant in the supine position after a 6-hour fast. Values are expressed as the medians (95% CIs). Values in the children without cirrhosis are presented for reference. PV hypoplasia is defined as an internal PV diameter ≤ 4 mm, regardless of patient age. The pathologic pretransplant PV flow is defined as fluctuant, absent, or hepatofugal.
*P results of comparison between patients with cirrhosis with and without BA.

TABLE 3. Correlations Between the Pretransplant Liver and Systemic Noninvasive Hemodynamic Parameters and the PELD Score in a Population of 52 Pediatric Patients Undergoing a Primary LT from a Living Related Donor at Cliniques Universitaires St Luc, Brussels, Belgium, Between March 2012 And October 2014

Pretransplant Doppler Ultrasound Hemodynamic Parameter (n = 52)	Kendall's tau	*P* Value
Internal PV diameter, mm	–0.4	<0.001
PV velocity, cm/second	–0.3	0.007
PV flow, mL/minute	–0.4	0.003
Cardiac index, L/minute/m^2	0.2	0.13 (NS)
Left ventricular ejection fraction, %	0.3	0.007

PV diameter than the children without cirrhosis (median, 4.3 [95% CI, 3.7-4.9] versus 5.9 [95% CI, 4.0-6.7] mm, respectively; $P = 0.047$). The children with cirrhosis also had a lower PV velocity (median, 15.5 [95% CI, 11.5-19.5] versus 28.5 [95% CI, 18-51] cm/second, respectively; $P = 0.007$), and a higher ARI (median, 0.9 [95% CI, 0.8-0.9] versus 0.7 [95% CI, 0.6-0.8], respectively; $P = 0.003$) at pre-LT Doppler ultrasound of the liver. When analyzing specifically cirrhosis with and without BA, abnormal liver hemodynamic parameters were mostly observed in children with cirrhosis with BA, as detailed in Table 2.

Pretransplant mean systemic arterial pressure, heart rate, respiratory rate, cardiac index, and left ventricular ejection fraction were similar in children without cirrhosis and children with cirrhosis, whether with or without BA (data not shown).

PELD score was negatively correlated with pretransplant PV diameter, PV velocity, and PV flow, and it was positively correlated with pretransplant left ventricular ejection fraction (Table 3).

INTRAOPERATIVE CARDIOPULMONARY MONITORING AND ASSESSMENT OF NATIVE LIVER HEMODYNAMICS USING INVASIVE METHODS

Patients with cirrhosis had a smaller extrahepatic external PV diameter (median, 6 mm; 95% CI, 5.5-6.5 mm) than children without cirrhosis (median, 8.5 mm; 95% CI, 7-10 mm; $P = 0.01$). As expected, these children also had a higher degree of portal hypertension (median PVP-CVP gradient, 14.5 mm Hg; 95% CI, 12.5-16 mm Hg), compared with patients without cirrhosis (median, 3.5 mm Hg; 95% CI, 1-4 mm Hg; $P < 0.001$). The PV flow into the native liver was significantly lower in children with cirrhosis (median, 12 mL/minute/100 g of liver; 95% CI, 6-16 mL/minute/100 g of liver) than in children without cirrhosis (64 mL/minute/100 g of liver; 95% CI, 56-71 mL/minute/100 g of liver; $P < 0.001$). Similarly, the total flow into the native liver was lower in patients with cirrhosis (median, 36 mL/minute/100 g of liver; 95% CI, 27-47 mL/minute/100 g of liver) compared with children without cirrhosis (median, 86 mL/minute/100 g of liver; 95% CI, 61-90 mL/minute/100 g of liver; $P = 0.002$). In contrast, the HA flow was similar in children with cirrhosis (median, 20 mL/minute/100 g of liver; 95% CI, 16-26 mL/minute/100 g of liver) and children without cirrhosis (median, 19 mL/minute/100 g of liver; 95% CI, 5-29 mL/minute/100 g of liver; $P = 0.93$, not significant [NS]). Accordingly, the cirrhotic livers were essentially

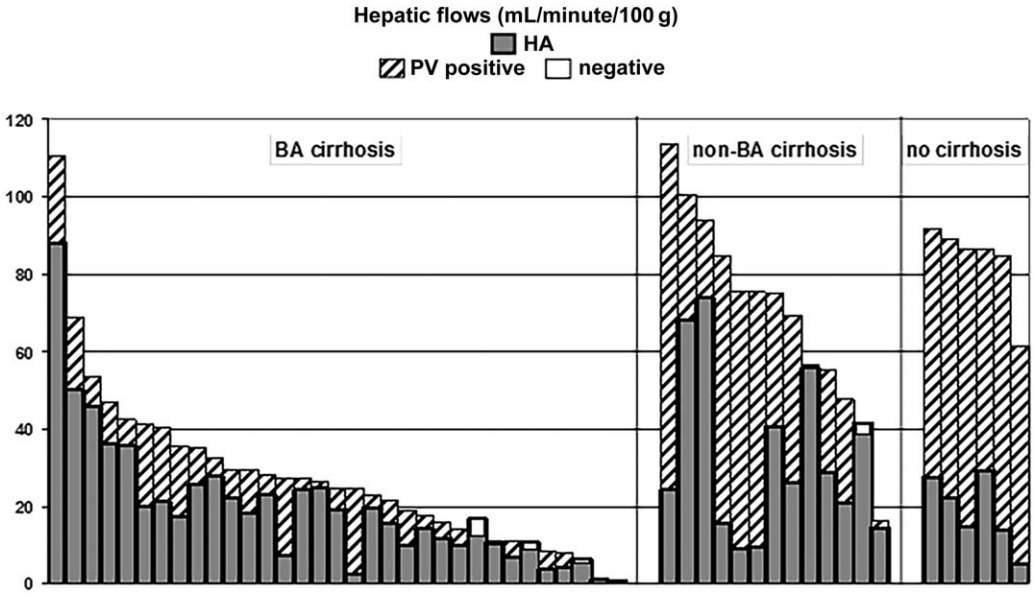

FIG. 1. Invasive native liver flows according to the pretransplant diagnosis in a population of 52 pediatric patients undergoing a primary LT from a living related donor at Cliniques Universitaires St. Luc, Brussels, Belgium, between March 2012 and October 2014. BA cirrhosis, n = 33; non-BA cirrhosis, n = 13; no cirrhosis, n = 6.

TABLE 4. Invasive Native Liver Hemodynamic Parameters According to the Pretransplant Diagnosis in a Population of 52 Pediatric Patients Undergoing a Primary LT From a Living Related Donor at Cliniques Universitaires St Luc, Brussels, Belgium, Between March 2012 And October 2014

Invasive Native Liver Hemodynamic Parameter	Patients With Cirrhosis Without BA (n = 13)	Patients With Cirrhosis With BA (n = 33)	*P* Value*	Children Without Cirrhosis (n = 6)
External PV diameter, mm	9 (7.0-10.5)	5 (4.7-5.5)	0.01	8.5 (7-10)
PV pressure, mm Hg	19 (15.0-23.5)	25.5 (24.5-27.0)	0.003	11.5 (10-13)
PVP-CVP gradient, mm Hg	12 (6.5-17.5)	15 (13.5-16.5)	0.14 (NS)	3.5 (1-4)
PV flow/100 g of liver, mL/minute	34 (16-54)	7 (4-11)	0.002	64 (56-71)
HA flow/100 g of liver, mL/minute	31 (18-47)	17 (13-22)	0.03	19 (5-29)
Total liver flow/100 g of liver, mL/minute	71 (52-85)	25 (19-31)	<0.001	86 (61-90)

NOTE: Values are expressed as the medians (95% CIs). Values in the children without cirrhosis are presented for reference.
**P* value results of comparison between patients with cirrhosis with and without BA.

perfused by arterial flow (median arterial flow/total liver flow, 67.3%; 95% CI, 57.8%-76.1%) in contrast with the noncirrhotic liver in which only 21.1% (95% CI, 8.1%-32.1%) of the flow was delivered by the HA ($P = 0.002$). As shown in Fig. 1 and Table 4, impaired native liver hemodynamic parameters as measured invasively were mostly observed in children with cirrhosis affected by BA. It is important to mention the statistically significant correlation between external PV diameter and age at LT (this correlation was linear up to the age of 7 years; data not shown).

Central venous pressure, mean arterial systemic pressure, heart rate, and cardiac index as measured intraoperatively were similar in children without cirrhosis and children with cirrhosis, whether or not with BA (data not shown).

PELD score correlated significantly with the decrease in the external PV diameter, the severity of portal hypertension, and the reduction of PV and total liver flows (Table 5). However, no correlations were found between systemic hemodynamic parameters and PELD score.

A significant correlation was found between noninvasive and invasive measures of extrahepatic PV diameter (Kendall's tau = 0.5; $P < 0.001$) and PV flow (tau = 0.5; $P < 0.001$).

TABLE 5. Correlations Between Invasive Liver and Systemic Hemodynamic Parameters and the PELD Score in a Population of 52 Pediatric Patients Undergoing a Primary LT From a Living Related Donor at Cliniques Universitaires St Luc, Brussels, Belgium, Between March 2012 And October 2014

Intraoperative Hemodynamic Parameter (n = 52)	Kendall's tau	*P* Value
External PV diameter, mm	−0.3	0.001
PV pressure, mm Hg	0.5	<0.001
PVP-CVP gradient, mm Hg	0.4	<0.001
PV flow/100 g of liver, mL/minute	−0.4	<0.001
HA flow/100 g of liver, mL/minute	−0.02	0.84 (NS)
Total liver flow/100 g of liver, mL/minute	−0.3	<0.001
HA flow/total liver flow, %	0.3	<0.001
PV flow/total liver flow, %	−0.3	<0.001
Cardiac index, L/minute/m^2 (n = 28)	0.1	0.63 (NS)
Cardiac flow, mL/minute (n = 28)	−0.2	0.27 (NS)

HISTOLOGICAL STUDIES ON NATIVE LIVERS AND PVS

As expected, all patients with cirrhosis had a METAVIR equivalent score of 4. The Laennec score was determined for subclassification of cirrhosis. A total of 24 of the children with BA (24/33 = 72.7%) had a Laennec score of 4C, compared with only 4 of the other patients with cirrhosis (4/13 = 30.8%; $P = 0.002$). Compared with non-BA cirrhosis, BA patients also had a higher CPA in their native liver (morphometry in Sirius red stained sections; median, 34.4% [95% CI, 27.5%-42.6%] versus 41.3% [95% CI, 36.6%-46.8%], respectively; $P = 0.03$). Little collagen was found in noncirrhotic livers (median, 13%; 95% CI, 10.1%-21.2%). A significant correlation was also found between Laennec score and native liver CPA ($P < 0.001$). In contrast to other etiologies of cirrhosis, BA was associated with a reduction in the caliber of intralobular PV, as confirmed by the mean HA/PV lumen ratio of 0.7 ± 0.04; this ratio was significantly higher than the ratio measured in non-BA cirrhotic samples (0.3 ± 0.05; $P < 0.001$) or in noncirrhotic livers (0.2 ± 0.04).

The extrahepatic PV intima/total wall thickness ratio was significantly higher in BA children (median, 0.5; 95% CI, 0.4-0.5) compared with other children with cirrhosis (median, 0.07; 95% CI, 0.0-0.2; $P < 0.001$) or to children without cirrhosis (median, 0.06; 95% CI, 0.0-0.1; Fig. 2).

CPA was negatively correlated with PV diameter, PV flow, and total liver flow ($P = 0.01$; $P = 0.02$; $P = 0.005$; respectively; data not shown).

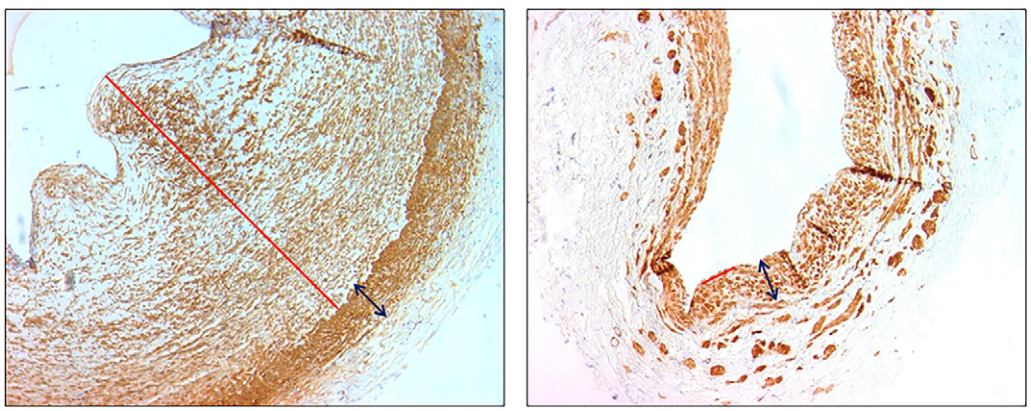

FIG. 2. Perpendicular histological section of extrahepatic PV in a BA patient (left) showing the important thickening of the intima (red line) in case of PV hypoplasia, compared with the normal wall of extrahepatic PV in a non-BA child with cirrhosis without PV hypoplasia (right). Tunica media is indicated by blue arrows. Alpha-actin smooth muscle immunostaining (original magnification × 10).

TABLE 6. Noninvasive Native Liver Hemodynamic Parameters as Predictive Factors of the Need to Use the Portoplasty Technique for PV Reconstruction During the LT Procedure in a Population of 52 Pediatric Patients Undergoing a Primary LT From a Living Related Donor at Cliniques Universitaires St Luc, Brussels, Belgium, Between March 2012 And October 2014

Native Liver Doppler Ultrasound Hemodynamic Parameter	Cutoff Value	*P* Value	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Internal PV diameter, mm	≤4	<0.001	84.2	70	64	87.5
PV velocity, cm/seconds	<11	<0.001	73.7	90	82.4	84.4
Hepatic ARI	>0.8	0.001	94.7	56.7	58.1	94.4
Mean HA velocity, cm/seconds	>46	0.3 (NS)	66.7	54.8	50	70.8

NONINVASIVE LIVER HEMODYNAMIC PARAMETERS AND PREDICTION OF THE TYPE OF PV RECONSTRUCTION DURING LT

A total of 21 patients with an external PV diameter ≤ 5 mm (as measured intraoperatively) and/or a sclerotic wall appearance required a portoplasty for PV reconstruction during the LT procedure, including 2 children with non-BA cirrhosis (2/13 = 15%) and 19 with BA cirrhosis (19/33 = 58%; $P = 0.02$). In children who met the intraoperative criteria for portoplasty, pretransplant Doppler data had already predicted significantly smaller internal PV diameter (median, 3.4 [95% CI, 3-4] versus 5.2 [95% CI, 4.5-6] mm in those who did not meet the criteria and had an end-to-end anastomosis; $P < 0.001$). Similarly, children who needed portoplasty had a lower PV velocity as measured by pre-LT Doppler ultrasound (median, 7.5 cm/seconds; 95% CI, −6 to 16 cm/seconds) than the other patients (median, 21 cm/seconds; 95% CI, 17.5-26.0 cm/seconds; $P < 0.001$). The pretransplant ARI was also higher in children requiring portoplasty (median, 0.9 [95% CI, 0.9-1.0] versus 0.8 [95% CI, 0.8-0.9] in children with classical anastomosis; $P = 0.002$). Pretransplant liver hemodynamic parameters collected by Doppler ultrasound appear to be good predictive factors of the need to use portoplasty technique for PV reconstruction during the LT procedure (Table 6).

Discussion

This work showed a 60% reduction of the total liver flow in children with cirrhosis, with an increase of the percentage of HA contribution to total liver flow (median arterial flow/total liver flow, 67.3%). In contrast, under physiological conditions, the normal liver mainly receives its blood supply through the PV (75%-80%), the remaining 25% being delivered through the HA. Total hepatic blood flow in adults ranges between 800 and 1200 mL/minute, which corresponds to approximately 100 mL/minute/100 g of liver wet weight.[29] Our data suggest that the children without cirrhosis are within these physiological ranges. Physiologically, changes in PV flow are compensated for by changes in HA flow, according to the so-called hepatic artery buffer response (HABR).[29] In adults, several studies have observed that native flows through the cirrhotic liver are characterized by a low PV flow and a concomitant increase in the HA flow.[20,30] The same phenomenon has been observed in a single pediatric study including 53 patients.[31] However, to date, whether HABR is preserved in patients with cirrhosis and is dependent on the stage of liver disease is unclear. Several studies have shown an increased hepatic arterial resistance in adults with cirrhosis, related to the degree of portal hypertension, portal resistance, and Child-Pugh score.[32-34] In contrast, Kleber et al. reported an increased hepatic arterial flow in Child-Pugh class C adult patients, suggesting that HABR might be independent of the liver disease stage.[35] In our series, the children with cirrhosis had a significantly smaller external PV diameter (median, 6 mm), a higher degree of portal hypertension (median PVP-CVP gradient, 14.5 mm Hg), and a greater reduction of PV flow (median, 12 mL/minute/100 g of liver) than the children without cirrhosis, but they did not have a significant increase in HA flow (median, 20 mL/minute/100 g of liver). Thus, the HABR response did not seem to be operating in our children with cirrhosis.

Advances in orthotopic LT have increased the safety and success of the procedure in children. A key determinant of outcome is the patency of vascular anastomoses. Prior knowledge of the PV, HA, and inferior vena cava status can enable surgeons to improve their procedure plans and anticipate the need for vascular reconstruction. A detailed Doppler ultrasound examination of the hepatic vasculature by an experienced radiologist has been considered as providing sufficient vascular imaging for most children scheduled for LT.[36] In our work, liver hemodynamic parameters were studied preoperatively using Doppler ultrasound and intraoperatively using transit time flowmetry. Even if Doppler ultrasound is limited by a lack of reproducibility and accuracy due to intraobserver, interobserver, and interequipment variability,[37] a good correlation was observed in our study between the 2 methods for pretransplant evaluation of extrahepatic PV diameter and PV flow (even if PV flow calculation necessitates a perpendicular angle between the long axis of the PV and the Doppler beam, and requires a precise PV diameter measurement).

We also observed that alterations of liver hemodynamic parameters (collected using Doppler ultrasound and/or invasive flowmetry) were correlated with the clinical degree of cirrhosis (PELD score) and the histological severity of fibrosis (native liver CPA). This finding was also reported in the work of El-Shabrawi et al., which showed a reduction in PV flow velocity using Doppler ultrasound according to Child-Pugh classification in a pediatric population.[38] Considering these results, cirrhosis in children may also be considered as a hemodynamic disease of the liver. According to our clinical experience in more than 1000 LTs in children at our center, noninvasive hemodynamic parameters collected preoperatively using Doppler ultrasound may be considered as additional elements for evaluation of the degree of emergency for LT.

Despite their younger ages, our BA patients had a more severe degree of clinical cirrhosis and histological fibrosis. BA is characterized by portal fibrosis, progressively linking portal areas that may dramatically progress to secondary biliary cirrhosis within a few weeks after birth.[39] Our work suggested that children with BA had more severe reduction of PV flow and total liver flow than other children with cirrhosis. This observation could be explained by a more intense fibrosis concentrated in the portal areas, surrounding intrahepatic PV and HA, and narrowing the vascular spaces. Accordingly, from a clinical perspective, the livers of patients with BA seem to be severely hypoperfused and at risk for liver necrosis in the event of hypotension.[10,40]

Adult patients with liver cirrhosis and portal hypertension usually develop a hyperdynamic circulatory syndrome, with high cardiac output, heart rate, and total blood volume and with reduced total systemic vascular resistance and arterial pressure.[41,42] They also have a cirrhotic cardiomyopathy, with an increased baseline cardiac output.[43] Whether similar hemodynamic adaptations occur in children with cirrhosis is not well documented. A study comparing 2-dimensional echocardiography parameters between 22 children with cirrhosis and 22 age-sex matched controls showed no significant differences in left ventricular ejection fractions.[44] In contrast, a recent study evaluating the cardiovascular status of 40 children with BA listed for LT showed abnormal 2-dimensional echocardiography parameters in 70% of patients compared with well-matched controls.[2] In our study, the assessment of systemic hemodynamics during the pre-LT period using either noninvasive (echocardiography) or invasive methods (transpulmonary thermodilution) showed no significant differences between patients without cirrhosis and patients with cirrhosis, with or without BA. This could be explained by the young age of our population (median age at transplantation was 1 year). One explanation of this observation might be that these young children do not have a prolonged history of cirrhosis, and therefore, do not have the time to develop a hyperdynamic circulatory syndrome (characteristic of adults with cirrhosis).

As observed in our study and in other works, PV hypoplasia is characteristic of children with BA.[7,14,45] Saad et al. described a mild to severe fibrosis and thickening of the extrahepatic PV at the time of transplantation in 80% of patients with BA and previous portoenterostomy.[46] The present work showed that thickening of the extrahepatic PV wall is concentrated at the intima and represents a unique characteristic of BA, not observed in non-BA children with cirrhosis. Additionally, morphological alterations extend to the intrahepatic PV with critical narrowing of the intralobular PV lumen. To the best of our knowledge, this study is the first to describe these specific alterations of intrahepatic PV in children with BA. Morphologic changes of intrahepatic PV may be important additional elements for the diagnosis of BA.

Many publications have reported the rate and management of PV complications after pediatric living donor LT.[47-49] Well-documented risk factors for PV thrombosis include small, hypoplastic, or sclerotic PV,

which are usually associated with young age or low recipient body weight, commonly seen in BA patients.[12,13] We previously reported that the laterolateral portoplasty technique for PV reconstruction during LT could be used with good results in case of PV hypoplasia.[14] Most of the children requiring a portoplasty in the present study were affected by BA. We observed that several of the pretransplant liver hemodynamic parameters, collected using Doppler ultrasound, seemed to be good predictors of the need to use the portoplasty technique for PV reconstruction during LT. Therefore, according to the hemodynamic parameters described by radiologists in the pretransplant period using Doppler ultrasound, surgeons could have prior knowledge of the techniques that should be used during the transplant procedure, particularly for PV reconstruction.

In conclusion, liver hemodynamics are impaired in children with cirrhosis, particularly in patients with BA. These alterations are correlated to the clinical severity of cirrhosis and the histological severity of fibrosis. Preoperative Doppler ultrasound provides similar appraisal of the hemodynamics as intraoperative measurements. In contrast to adults, children with cirrhosis do not seem to develop a hyperdynamic circulatory syndrome at the time of LT. Hypoplasia and fibrosis of intrahepatic and extrahepatic PV characterize patients with BA. Our study confirmed that a detailed Doppler study of the native liver by an experienced pediatric radiologist seems to be a reliable tool to assist surgeons in planning the procedure and anticipating the type of vascular reconstruction needed, particularly for PV reconstruction.

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