Pediatr Radiol (2008) 38:403–408
DOI 10.1007/s00247-007-0733-5

ORIGINAL ARTICLE

Real-time and Doppler US after pediatric segmental liver transplantation

I. Portal vein stenosis

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Received: 2 August 2007 / Revised: 13 November 2007 / Accepted: 7 December 2007 / Published online: 23 January 2008

Abstract
Background Accurate diagnosis of portal vein (PV) stenosis by real-time and color Doppler US (CD-US) after segmental liver transplantation in children can decrease morbidity by avoiding unnecessary biopsy, PV hypertension, thrombosis and loss of the graft.
Objective To evaluate CD-US parameters for the prediction of PV stenosis after segmental liver transplantation in children.
Materials and methods We retrospectively reviewed 61 CD-US examinations measuring the diameter at the PV anastomosis, velocities at the anastomosis (PV1) and in the segment proximal to the anastomosis (PV2), and the PV1/PV2 velocity ratio. The study group comprised patients with stenosis confirmed by angiography and the control group comprised patients with a good clinical outcome.
Results PV stenosis was seen in 12 CD-US examinations. The mean PV diameter was smaller in the study group (2.6 mm versus 5.7 mm) and a PV diameter of <3.5 mm was highly predictive of stenosis (sensitivity 100%, specificity 91.8%).
Conclusion A PV diameter of <3.5 mm is a highly predictive CD-US parameter for the detection of hemodynamically significant stenosis on angiography.

Keywords Color Doppler US · Portal vein stenosis · Pediatric segmental liver transplantation · Venous complication · Hepatic vein stenosis

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Introduction

The incidence of portal vein (PV) complications (thrombosis and stenosis) after liver transplantation in children is higher than in adults [1–6], especially after living-related liver transplantation [4–7]. The reported incidence of PV stenosis varies between 0% and 30% [1, 3–9], compared to 1.3% in adults [10]. Early and accurate diagnosis of PV stenosis is desirable because it can progress to PV hypertension,

thrombosis and loss of the liver graft if left untreated. US, both real-time and Doppler (CD-US), is the initial imaging modality for detection and follow-up of early and delayed vascular and nonvascular complications after liver transplantation. With an accurate diagnosis of PV stenosis by CD-US unnecessary biopsy and institution of therapy and further development of portal hypertension, gastrointestinal bleeding and organ damage can be avoided leading to a decrease in morbidity.

There are a paucity of data about the diagnosis of PV complications by CD-US following liver transplantation in children, even though its role in the diagnosis of hepatic artery complications has been well established [11]. The purpose of this study was to evaluate CD-US parameters and assess their sensitivity and specificity for the prediction of PV stenosis after segmental liver transplantation in a pediatric population.

Materials and methods

Patients

The study was performed according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the hospital. Written informed consent was obtained in every case.

A total of 77 CD-US examinations were performed according to an established protocol in 61 recipients of a liver transplant (32 girls/29 boys, average age 5.8 years, range 1.2–15.4 years) from January 2002 through January 2006. Of the patients in the control group, 12 had multiple CD-US examinations (8 patients had two and 4 patients had three each). For these patients, the mean value of each parameter was calculated and included as one CD-US examination. Thus, 61 CD-US examinations (study group 12, control group 49) were analyzed retrospectively. The study included 33 living-donor liver transplantations and 28 cadaveric split-liver transplantations imaged from the first day to 12 years (mean 15 months). All children in our series had direct vascular anastomosis and no venous conduits were used. The PV of the donor was larger than the PV of the recipient in all cases. Children with stenosis confirmed by angiography were included in the study group and those with a good clinical outcome were included in the control group. Exclusion criteria included the presence of a stent or thrombosis in the PV prior to the study.

Algorithm for investigation

Sonograms were acquired as part of the regular follow-up examination of the liver transplants or whenever symptoms of vascular complications were suspected on the basis of clinical findings, such as upper gastrointestinal bleeding, ascites, pleural effusion, splenomegaly or thrombocytopenia, or abnormal liver function tests. The CD-US examinations that showed stenosis (included in the study group) were confirmed by angiography, and the examinations that showed no abnormality (included in the control group) were confirmed by a good clinical outcome, based on liver function tests during the 49 months of the study period. The angiographic criterion for PV stenosis was a gradient pressure greater than 5 mmHg between the segments proximal and distal to the anastomosis. In 12 patients the CD-US examination was correlated with portography.

Doppler US technique and interpretation

CD-US examinations were performed by the same pediatric radiologist using a SSD-2000 multi-view scanner (Aloka, Tokyo, Japan), or a Logiq 500 or Logiq 7 scanner (GE Medical Systems, Milwaukee, WI) with a convex probe of 5.0 or 2.0–5.0 MHz. All examinations were performed with the child in the supine or left lateral decubitus position, without breath-holding or sedation. Patients had usually fasted for 2 or 3 h prior to the examination. Images of the spectral Doppler waveform of the veins and the PV diameter in the long axis were obtained at least twice in each examination. The angle-corrected highest peak velocity was measured in two segments of the vein: the narrowest point of the PV anastomosis (PV1) and 1–2 cm proximal to the PV anastomosis (PV2). The ratio between the two velocities was calculated (PV1/PV2 velocity ratio).

Statistical analysis

The demographic and clinical characteristics of the patients are summarized with frequency counts, means, standard deviations, medians and ranges. First, the frequency and variability of each potential parameter in relation to outcome were evaluated. Diagnostic parameters were then compared between the study group and the control group via *t*-tests for independent groups (the equality of the variances between the stenosis group and control groups was tested with the folded F method and appropriate *t*-tests were performed). Finally, the cutoff scores that achieved maximum sensitivity and specificity, accounting for positive and negative predictive values, were determined. Results were generated in terms of receiver operating characteristic (ROC) curves and optimal cutoff scores were generated for clinical use. All statistical tests were two-tailed and their significance level was set at 0.05. The results were also compared with those of published studies.

Results

Clinical symptoms of PV stenosis (upper gastrointestinal bleeding, ascites, pleural effusion, splenomegaly) or abnormal liver function tests were seen in 12 patients 2 weeks to 20 months after transplantation. The reported time between transplantation and clinical presentation of PV stenosis in the literature is 1 day to 105 months [2, 4–6]. Portography confirmed this vascular complication in all of them. The diameter of the PV at the anastomosis site was narrower in the study group (mean±SD 2.6±0.7 versus 5.7±2.3, $P<0.001$) and the PV1 velocity and PV1/PV2 velocity ratio were higher in the study group (165.1±38.7 versus 76.0± 41.8, $P<0.001$, and 4.5±3.8 versus 1.6±0.8, $P=0.022$, respectively; Table 1 and Fig. 1) than in the control group. There was no significant difference in the PV2 velocity between the groups (49.6±23 cm/s in the study group and 47.5±15.5 cm/s in the control group, $P = 0.779$). Dilatation of the PV distal to the anastomosis was present in all patients with stenosis, and was also observed in some patients in the control group.

After treatment, the diameter of the PV and the PV1/PV2 velocity ratio returned to values within the range of values in the control group (Fig. 2).

Three CD-US examinations performed within 10 days of transplantation showed PV diameters <3.5 mm, which normalized after 3 weeks (PV diameter >5.0 mm) with no clinical or laboratory abnormalities at the time of the examination. These patients were included in the control group.

Statistical analysis showed the following to be predictive of stenosis: a PV diameter <3.5 mm (sensitivity 100%, specificity 91.8%), a PV1 velocity of >106 cm/s (sensitivity 100%, specificity 79.6%), and a PV1/PV2 velocity ratio of >2.4 (sensitivity 75%, specificity 85.7%; Fig. 3).

Discussion

Cadaveric split-liver and living-donor liver transplantation is mostly performed in children [7, 12] and the higher incidence of venous stenosis after segmental liver transplantation in children might be explained by technical difficulties related to the relatively short donor vein and size discrepancy at the anastomotic site. In general, the most accepted CD-US criterion for PV stenosis is an increase in velocity of more than three- to fourfold at the stenosis site relative to that in the segment proximal to the stenosis [13–16]. A high PV1 velocity (>100 cm/s) has been reported to indicate significant stenosis of the veins after liver transplantation in adults [17]. In children, a PV diameter of 2.5 mm or less and/or a flow acceleration at the stricture with a poststenotic jet have been reported in PV stenosis [6]. The sensitivity and specificity of these criteria have not been reported, to the best of our knowledge.

The cutoff values for the CD-US parameters for PV stenosis reported in the literature are somewhat different from ours. In our study, a PV diameter of 3.5 mm showed the best diagnostic performance of all the parameters studied, with a sensitivity of 100% and a specificity of 91.8% (CI 0.91–0.99). We selected cutoff values by first noting that screening studies benefit from having a high sensitivity to avoid false-negative results. To the best of our knowledge, no studies have addressed this issue except for raw data. Lee et al. [6] studied 18 patients with PV stenosis among 167 children with liver transplantation and determined a PV diameter <2.5 mm as a cutoff value for stenosis. If this value had been applied to our results, the sensitivity would have dropped to 42% and the specificity would have increased to 100%. This discrepancy between the statistical results can be explained by the fact that the main factor in the decision to carry out angiography in our study was the clinical evaluation, and angiography was considered appropriate in patients with few symptoms. In this way, children with less significant stenosis could be identified.

It is important to point out that stenosis represented by a PV diameter of <3.5 mm in the early postoperative period (within 10 days) in the absence of laboratory or clinical abnormalities can be transient and caused by surgical edema. Another consideration is that the normal range of PV diameters in healthy children is age-dependent. The normal limit for PV diameter in the healthy neonate is 3.0 mm, and the normal range in a patient at 12 months of age (the age of the youngest patient in our study) is 4.0 to

Table 1 Doppler US parameters for the PV in the study and control groups

Parameter	Study group (n=12)		Control group (n=49)		P value
	Mean±SD	Range	Mean±SD	Range	
PV diameter (mm)	2.6±0.7	1.7–3.5	5.7±2.3	2.5–13.0	<0.001
PV1 velocity (cm/s)	165.1±38.7	107.1–230.0	76.0±41.8	17.4–188.0	<0.001
PV2 velocity (cm/s)	49.6±23.0	13.0–94.6	47.5±15.5	23.8–86.7	0.779
PV1/PV2 velocity ratio	4.5±3.8	1.8–15.4	1.6±0.8	0.6–3.7	0.022

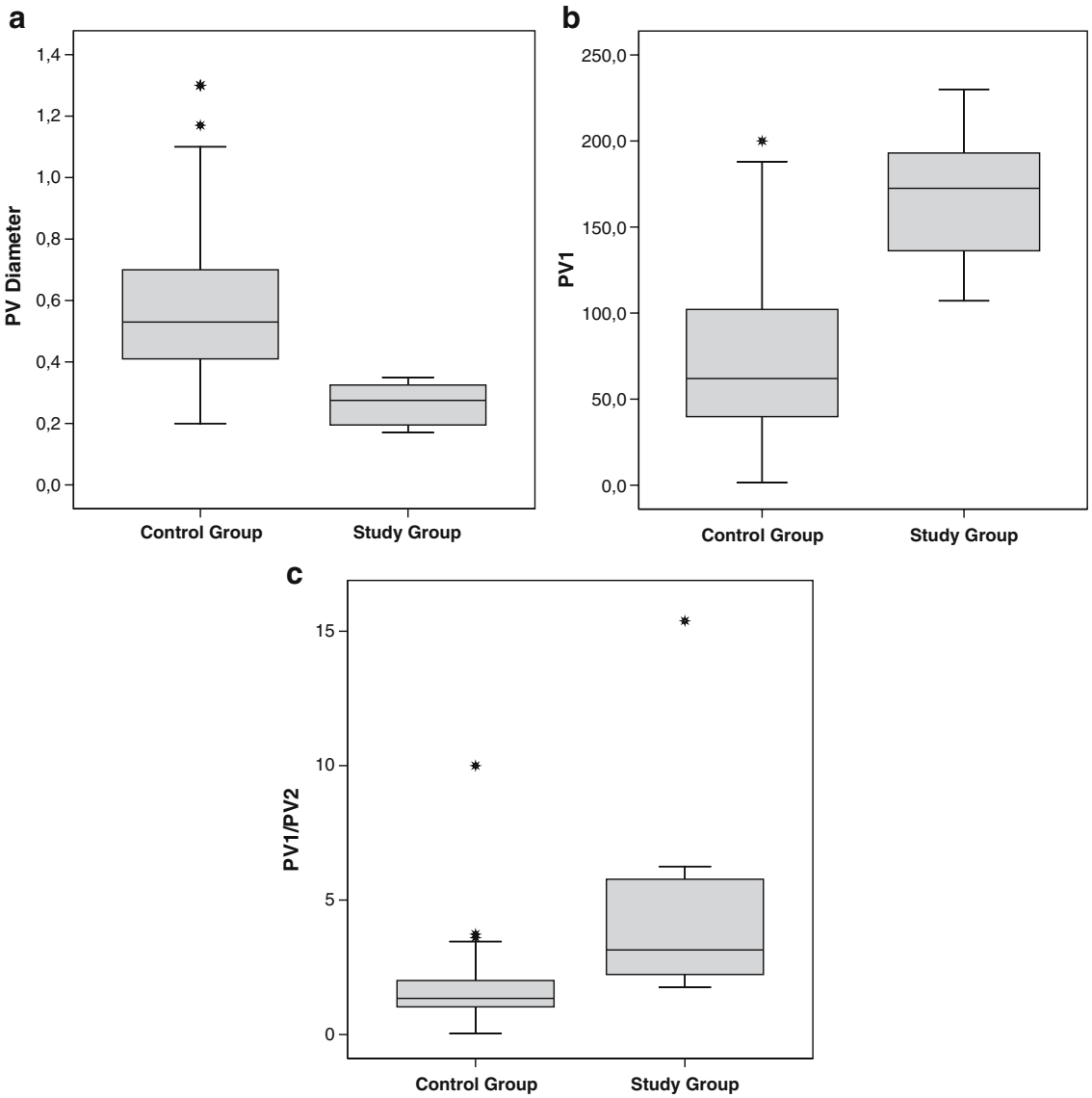

Fig. 1 Doppler US parameters in the study and control groups: **a** diameter of the PV at the anastomosis, **b** PV1 velocity, **c** PV1/PV2 velocity ratio

8.0 mm [18]. Dilatation of the PV distal to the anastomosis was present in all patients in the study group and in some patients in the control group. Dilatation of the PV distal to the anastomosis in the control group could have been a result of focal narrowing of the PV at the anastomosis that can occur because of size discrepancy between the donor and recipient veins [19]. This narrowing could also be seen indirectly by the higher velocity at PV1 compared to that at PV2 in the control group. Although this focal narrowing is not indicative of stenosis [19], it probably results in turbulent flow immediately distal to the anastomosis, resulting ultimately in dilatation in the segment distal to the anastomosis with time [20].

A high PV1 velocity of >100 cm/s has been reported to indicate PV stenosis, but there are no further details about the study [17]. In our study, a PV1 velocity of >106 cm/s showed a sensitivity of 100% and a specificity of 79.6%, 95% CI (0.86–0.98) for PV stenosis. This value is not very different from the one previously reported, but it is more specific. If a PV1 velocity of >100 cm/s had been applied, the sensitivity would also have been 100%, but the specificity would have dropped to 73.5%. Despite the fact that PV1/PV2 velocity ratios of >3.0 and >4.0 are the most widely accepted parameters for PV stenosis, a PV1/PV2 velocity ratio of >2.4 showed a sensitivity of 75% and a specificity of 85.7%, 95% CI (0.81–0.97). If a PV1/PV2 velocity ratio of >3.0 or >4.0 had been applied, both previously described [13–16], the sensitivity/specificity would have been 50%/90% and 42%/100%, respectively. Therefore, the cutoff values chosen for the PV1 velocity and the PV1/PV2 velocity ratio were those that showed the best results in terms of sensitivity and specificity.

In conclusion, a PV diameter <3.5 mm was shown to be the most sensitive and specific single parameter for

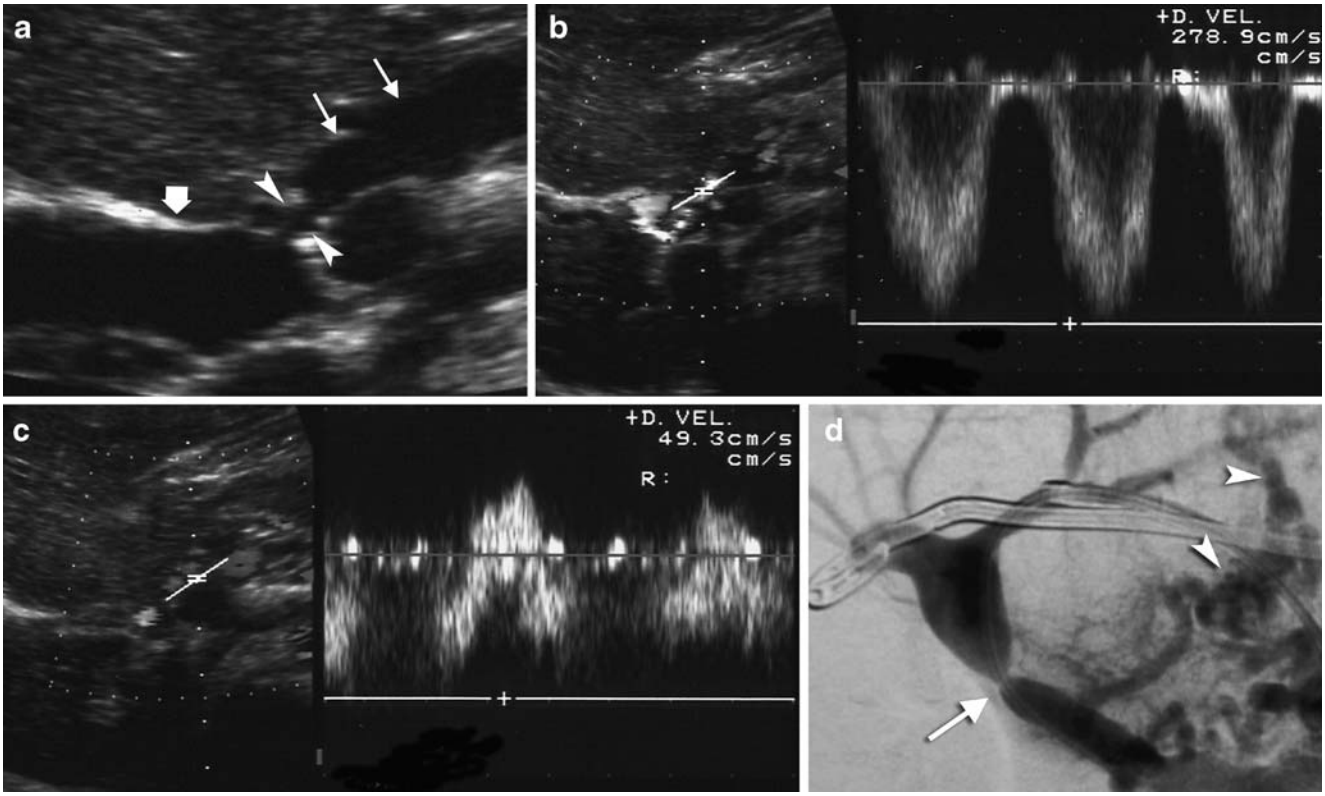

Fig. 2 A 3½-year-old boy with a living-donor liver transplant who presented with upper gastrointestinal bleeding. **a** CD-US image shows severe stenosis (2.2 mm) at the anastomosis (*arrowheads*) between the recipient PV (*thin arrows*) and donor PV (*wide arrow*). **b**, **c** CD-US images show a fivefold increase in velocity at the anastomosis (**b**) relative to the segment proximal to the anastomosis (**c**). **d** Angiography confirms PV stenosis at the anastomosis (*arrow*). Collateral veins caused by the portal hypertension are noted (*arrowheads*)

predicting PV stenosis. Nevertheless, in the early postoperative period we can hypothesize that this finding represents a transient stenosis caused by surgical edema, in the absence of clinical signs of portal hypertension. The time of presentation of PV stenosis is reported to be in the late posttransplantation period supporting this idea [8, 12]. Further studies with larger populations should determine a more precise cutoff.

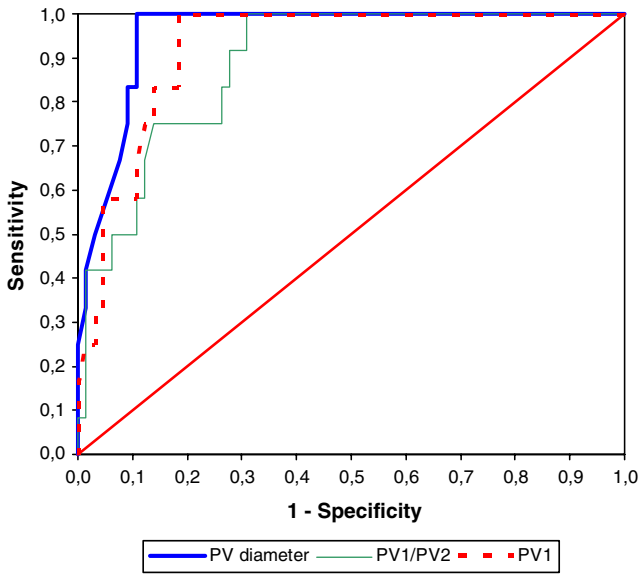

Fig. 3 Composite receiver operating characteristic curves show the variable performance of CD-US in detecting PV stenosis. Note that PV diameter shows the best sensitivity/specificity of all the variables

There were some limitations to this study. Normality in our control group was based on a good clinical outcome given that the CD-US parameters for the diagnosis of PV stenosis had not been established at the time of the study. Angiography was performed only in patients suspected of having portal or hepatic vein stenosis on the basis of clinical findings. Therefore, the majority of patients were not submitted to any kind of invasive procedure. This method might have led to the underrating of asymptomatic patients with PV stenosis, as there have been reports of PV stenosis on screening US in 11–67% of asymptomatic patients [2, 7, 10, 12, 14]. This was a preliminary study performed by one radiologist with the purpose of establishing a protocol in our institution as well as evaluating CD-US parameters and assessing their sensitivity and specificity for predicting venous stenoses after segmental liver transplantation in children. There are limitations in deriving ROC curves and cutoff values using small sample sizes because of consistent bias and overestimation of system performance. Further studies using a larger number of patients with interobserver variability analysis are necessary to confirm our results.

Conclusion

Our results showed that the most accurate parameter for the diagnosis of PV stenosis after segmental liver transplantation in children is the diameter of the PV at the anastomosis. PV diameter is a measurement that is rapidly acquired and reproducible; however, in the early postoperative period, a small PV diameter might represent a transient stenosis caused by edema and should be managed conservatively in the absence of clinical findings.

Acknowledgement Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) - Brasília, DF, Brazil, provided funding for this study.

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