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Hepatic artery thrombosis following pediatric liver transplantation: Assessment of blood flow measurement in allografts

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Abstract: The purpose of this study was to define parameters which could be predictive of hepatic artery thrombosis, which continues to be a major complicating factor in pediatric liver transplantation. The hepatic blood flow of 14 pediatric liver patients (15 grafts) who weighed less than 15 kg was measured electromagnetically during orthotopic liver transplantation. The results of blood flow determination and the clinical data in 7 patients (8 grafts) who developed hepatic artery thrombosis were compared with those of 7 control patients. All patients with a hepatic arterial flow of less than 60 ml/min developed hepatic artery thrombosis (4/8 vs. 0/7; $p < 0.05$), and the patients with hepatic artery thrombosis exhibited higher total hepatic and portal vein flow per 100 gram of liver tissue (262 vs. 136 ml/min; $p < 0.001$ and 222 vs. 80 ml/min; $p < 0.025$, respectively) as well as longer cold preservation time (384 vs. 326 min; $p < 0.025$). The results of our study suggest that hepatic arterial flows of less than 60 ml/min are critical for the development of hepatic artery thrombosis, and that portal venous overflow and increased preservation times may contribute to the development of hepatic artery thrombosis.

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Hepatic artery thrombosis (HAT) continues to be a life-threatening complication of orthotopic liver transplantation (OLTx), especially in small children (1–3). The incidence of this devastating complication among pediatric OLTx recipients in several series varies from 11.8 to 25% (1–3), and the mortality has been as high as 50% (1). HAT also accounts for one of the main causes of retransplantation in children (2, 4). Although rejection, infection, and technical problems such as intimal flap have been implicated as the etiology of HAT (1–3), little is known about the pathogenesis of this entity, which may develop in an allograft even under ideal circumstances.

The purpose of this study was to determine the significance of the hemodynamics of the liver allografts as a predictive parameter for the development of HAT after OLTx in pediatric patients, and to correlate this with and to determine other clinically relevant factors.

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Patients and methods

Between July 1, 1987 and October 23, 1987, 39 pediatric OLTx were performed in 31 patients at the Children's Hospital of Pittsburgh. Of these, 25 allografts in 20 patients underwent electromagnetic flow measurement of the hepatic artery (HA) and the portal vein (PV) during OLTx. The selection of these patients was based primarily on the availability of sterile probes. Two of these grafts required allograft right lobectomy pretransplant for volume reduction. Among these 25 allografts, 8 grafts in 7 patients developed HAT, including both grafts with the allograft right lobectomy.

Recipients who weighed less than 15 kg were analyzed in this study, since the incidence of HAT following OLTx is much higher in small children than in adults or large children (1, 2), and since none of the allograft recipients who underwent blood flow analysis and who weighed over 15 kg developed HAT. Therefore, the clinical data and the results of flow measurements among the 7 patients (8 grafts) who developed HAT were compared with those of 7 recipients (control group)

who did not develop HAT following OLTx. Ten allografts were excluded from this analysis, due to recipient body weight over 15 kg in 7 (16 to 40 kg, mean 26 kg), immediately postoperatively primary graft non-function in 2 and thrombosis of the right HA due to technical reasons in 1, following vascular reconstruction of the traumatized and transected small right HA originating from the superior mesenteric artery for which reconstruction was performed by end-to-end anastomosis between the transected right HA and the donor splenic artery. Among 8 grafts with HAT, no obvious technical failure, such as anastomotic failure due to intimal flap or kinking of the HA, could be identified. The diagnosis of HAT was made either on exploratory laparotomy, or by the absence of HA flow on arteriography or on two consecutive doppler ultrasonograms. For all patients studied in this series, the donor allografts were harvested by the rapid perfusion technique (5) and preserved in Euro-Collins solution (4°C). Veno-venous bypass was not used in any of these patients. All patients were hemodynamically stable at the time of hepatic blood flow measurements. Immunosuppression consisted of Cyclosporine and corticosteroids, and episodes of severe allograft rejection were treated with Orthoclone OKT® 3 (Ortho Pharmaceutical Co., Raritan, NJ). Immediately postoperatively, all patients received low molecular weight dextran intravenously at 5 ml/h for 4 days and heparin 50 units/kg subcutaneously every 12 h. Also, aspirin 20 to 40 mg/d p.o. or per nasogastric tube were administered. The above anticoagulation or antiplatelet therapy was discontinued when the patient demonstrated clinical or laboratory evidence of coagulopathy, as manifested by intraabdominal bleeding requiring blood replacement or a prothrombin time of over 20 seconds for more than 12 h posttransplant.

Blood flow measurement

Blood flows in the HA and PV were measured with a square-wave electromagnetic flowmeter, Cliniflow II®, Model FM701D (Carolina Medical Electronics, Inc., King, North Carolina). Probes which fit the vessels snugly were selected for the measurement. A zero flow reference was obtained by placing the probes and an isolated ground in a plastic beaker filled with normal saline. At the time of flow measurement, the heart rate, blood pressure, central venous pressure, urine output and the dose of vasopressors were recorded. Cardiac output was not measured. However, none of the 14 patients studied showed any evidence of cardiogenic shock or hypovolemia at the time of blood flow measurement: All of them demonstrated stable systemic blood pressure without tachycardia for age, and maintained urine output over 0.8 ml/kg/min. None of them was on vasopressor support in excess of renal dose dopamine.

Clinical parameters

The pertinent clinical factors evaluated and compared between the two groups of patients studied included the age, the underlying liver disease, the number of allografts transplanted, the body weight, the donor to recipient body weight ratio, the HA diameter, the presence of HA anomalies, the methods of HA reconstruction, the cold preservation time, the intervals between PV and HA anastomosis, anticoagulation and the T-lymphocyte crossmatch. The donor-to-recipient body weight ratio in the 2 patients who underwent allograft right lobectomy and who developed HAT was excluded from the comparison.

Statistical analyses

Mann-Whitney's U and Chi-square tests were used for the statistical evaluation in this study.

Results

Table 1 lists the pertinent clinical and hepatic blood flow data in 7 patients (8 grafts) with HAT. The age ranged from 10 to 36 months with a mean of 18.8 months and 4 patients were male (57.1%). The body weight varied from 6.3 to 13.5 kg with a mean of 9.5 kg. The underlying liver disease in all patients was congenital biliary atresia. Case 7 had already undergone 2 OLTx and required the 3rd OLTx for rejection, and the 4th OLTx for HAT presenting as a bile leak from choledochojejunostomy. Case 3 exhibited zero flow in the HA on flow measurement but, since the HA pulse was palpable, no further attempt was made to reconstruct the HA, and a diagnosis of HAT was made on the 4th postoperative d.

The diagnosis of HAT was made between 2 and 15 d postoperatively, with a mean of 6.4 d. The diagnosis was made by exploratory laparotomy in 1, arteriogram in 4 and two consecutive doppler ultrasonograms in 3 cases. Of these 7 patients, 5 required retransplantation (71.4%) due to liver failure from HAT, and Case 4 is awaiting retransplantation at home. In Case 3, the HA was assumed to have recanalized (1), since repeated doppler ultrasonogram demonstrated patent HA and the liver function remains near normal.

In Case 6, anticoagulation was discontinued 12 h postoperatively because of intraperitoneal bleeding. Also, this patient developed acute cellular re-

Table 1. Clinical and flow data in patients with hepatic artery thrombosis

Case	Age (mo)/ Sex	Body Weight (kg)	Liver Disease	HA Flow (ml/min)	HA Flow/ 100 g Liver (ml/min)	PV Flow/ 100 g Liver (ml/min)	HA/PV Flow Ratio	Total Flow/ 100 g Liver (ml/min)	Post-operative Anti-cuagulation	Comments
1	21/M	9.2	CBA	205	103	275	0.45	378	full	HAT by US and AG (2)* OLTx II (2)*
2	10/M	6.3	CBA	50	33	–	–	–	full	HAT by US and AG (2)* OLTx II (9)*
3	17/F	8.8	CBA	0	0	265	0	265	full	HAT by US (4, 5)* discharged, well
4	24/M	12.4	CBA	140	93	334	0.28	427	full	HAT by US and AG, (2)* unsuccessful HA rec (2)* discharged, awaiting OLTx II
5	23/F	13.5	CBA	50	18	400	0.05	418	full	Intraoperative HAT, unsuccessful HA Rec HAT by US (8, 12) OLTx II (76)*
6	18/M	9.8	CBA	135	68	90	0.75	158	minimal	allograft rejection (7)*. HAT by US and AG (15)*, OLTx II (21)*
7a	18/F	7.5	CBA, s/p OLTx II, rejection	30	20	113	0.18	133	minimal	HAT on exploratory laparotomy for bile leak (4)*, OLTx IV (11)*
7b	19/F	8.8	CBA; s/p OLTx III, HAT	220	88	76	1.16	164	partial (dextran only)	HAT by US (14)*, died of progressive liver failure (25)*

( )* = postoperative day.
HA = heaptic artery; PV = portal vein; CBA = congenital biliary arterial; HAT = hepatic artery thrombosis; US = ultrasonography; AG = angiography; OLTx = orthotopic liver transplantation; HA Rec = heaptic artery reconstruction.

Table 2. Clinical and flow data in patients without hepatic artery thrombosis

Case	Age (mo)/ Sex	Body Weight (kg)	Liver Disease	HA Flow (ml/min)	HA Flow/ 100 g Liver (ml/min)	PV Flow/ 100 g Liver (ml/min)	HA/PV Flow Ratio	Total Flow/ 100 g Liver (ml/min)	Post operative anti-coagulation	Comments
1	48/M	14.3	CBA	215	43	80	0.54	123	partial	died of sepsis (40)*
2	30/F	12.7	CBA	200	49	78	0.63	127	full	discharged, well
3	33/F	12.0	CBA	80	25	–	–	–	full	discharged, well
4	10/F	10.5	CBA s/p OLTx II PGNFN	60	14	–	–	–	partial	died of intraabdominal abscess (30)*
5	11/M	8.1	CBA s/p OLTx, HAT	100	40	88	0.45	128	full	discharged, well
6	21/M	9.2	CBA s/p OLTx, HAT	100	40	96	0.42	136	full	discharged, well
7	18/M	9.8	CBA s/p OLTx, HAT	405	108	56	1.93	164	none	died of CMV pneumonia (14)*

( )* = postoperative day.
HA = hepatic artery; PV = portal vein; CBA = congenital biliary atresia; OLTx = orthotopic liver transplantation; PGNFN = primary graft non-function; HAT = hepatic artery thrombosis.

Table 3. Comparison of clinical data between patients with and without hepatic artery thrombosis

	Patients		
	With HAT (n=8)	Without HAT (n=7)	p Value
Age (mo)	18.8±4.3*	24.4±13.6	NS
Diagnosis	CBA (8)+	CBA (7)+	NS
No. of allografts (I/II/III/IV)	6/0/1/1	3/3/1/0	NS
Body weight (Kg)	9.5±2.4	10.9±2.2	NS
Donor/recipient body weight ratio	0.81±0.22 (6)+	1.00±0.12	NS
HA diameter (mm)	4.5±1.0	4.5±0.6	NS
Arterial anomalies	right and left branch (2)+	right branch (1)+ right, left and PSB (1)+	
HA anastomosis (donor-recipient)	CA-CA (2)+ Ao-CA (1)+ CA-CHA (3)+ CA-Ao (2)+	CA-CA (3), CA-Ao (3)+ PSB-CA (1)+	NS
Cold ischemia time (min)	384±77	326±47	p<0.025
Interval between PV and HA anastomosis (min)	64±30	46±14	NS
Anticoagulation (full)	5/8	4/7	NS
T-lymhocyte crossmatch (positive/total)	2/6	1/7	NS

* mean±S.D.; ( )+ = number of patients; HAT = hepatic artery thrombosis; CBA = congenital biliary atresia; PSB = pulmonary sequestration branch; HA Rec = hepatic artery reconstruction; CA = celiac axis; Ao = aorta; CHA = common hepatic artery; HA = hepatic artery; PV = portal vein.

jection proven by percutaneous liver biopsy on the postoperative d 9, for which Orthoclone OKT® 3 was administered. HAT in this patient was identified 6 d later. In the other 6 patients, no evidence of rejection was observed or documented postoperatively. Of the 5 grafts with HAT which were replaced later (Case 1, 2, 5, 6 and 7a), 1 (Case 7a) whose HAT was diagnosed on posttransplant d 4 exhibited mild acute cellular rejection, which was considered to be due to reduction in immunosuppression for bile peritonitis from the disruption of the choledochojejunostomy secondary to HAT. Case 6, who was the only patient who demonstrated clincial evidence of acute cellular rejection, showed no evidence of rejection in the replaced allograft.

Cases 2 and 6 underwent allograft right lobectomy for volume reduction at the back table prior to revascularization.

Table 2 shows the pertinent clinical and hepatic blood flow data in 7 patients without HAT (control). Four patients are alive and well at home, whereas the other 3 patients died of infectious complications. None of them demonstrated clinical or histological evidence of rejection.

The clinical data for the patients with and without HAT are compared in Table 3. The cold ischemia time of the allograft was longer in the patients with HAT ($p<0.025$). Otherwise, no statistically significant difference could be identified in the age, the original diagnosis, the number of allografts transplanted, the recipient body weight, the donor-to-recipient body weight ratio, the HA diameter, the presence of HA anomalies, the interval between PV and HA anastomoses, postoperative anticoagulation, and the T-lymphocyte crossmatch. Although statistical significance was not achieved, HA anastomosis at the level of the recipient common HA with or without splenic artery ligation was performed in 3 out of 8 allografts with HAT, while all patients without HAT underwent either celiac axis to celiac axis anastomosis with splenic

Table 4. Comparison of the results of blood flow determinations between patients with and without hepatic artery thrombosis

	Patients		
	With HAT (n=8)	Without HAT (n=7)	p Value
HA flow (ml/min)	103.8±82.8*	165.7±121.1	NS
HA flow (ml/min)/100 g liver	52.9±39.8	45.6±30.0	NS
PV flow (ml/min)/100 g liver	221.9±128.8 (7)+	79.6±15.0 (5)+	p<0.025
HA/PV flow ratio	0.37±0.40 (7)+	0.79±9.64 (5)+	NS
Total hepatic flow (ml/min)/100 g liver	261.8±127.9 (7)+	135.6±16.6 (5)+	p<0.01

* Mean±S.D.; ( )+ = number of patients; HAT = hepatic artery thrombosis; HA = hepatic artery; PV = portal vein.

artery ligation, or donor celiac axis to recipient aorta anastomosis with interposition of a donor iliac artery (6).

Table 4 compares the blood flow data in patients with and without HAT. Although no statistically significant difference was seen in the HA flow per 100 g of liver tissue, the PV flow per 100 g of liver tissue ($p < 0.025$) and the total hepatic blood flow per 100 g of liver tissue ($p < 0.01$) were both significantly greater in those patients with HAT. The HA to PV flow ratio and the absolute HA flow tended to be lower in patients with HAT. All 4 grafts with an absolute HA flow of less than 60 ml/min at the time of flow measurement went on to develop HAT (4/8 vs. 0/7; $p < 0.05$, $\chi^2 = 4.77$).

Discussion

The high incidence of HAT after OLTx among small pediatric patients in this series is consistent with previous reports (1–3). Klintmalm et al. (7) reported, in adult OLTx recipients, the results of blood flow measurements which showed no significant correlation between the HA flow and the incidence of HAT. However, our study among pediatric OLTx patients weighing less than 15 kg demonstrated a 100% incidence of HAT in allografts where the HA flow was less than 60 ml/min. Furthermore, there was a significantly higher total hepatic as well as PV flow per 100 g of liver tissue in patients with HAT after OLTx. These parameters were observed in the absence of any significant difference in the clinical features other than the cold ischemia time between the two groups of patients.

A reciprocal relationship in the blood flow between the HA and PV, in the innervated or denervated liver, is a known phenomenon (8, 9), and it is suggested that portal overflow may increase the vascular resistance to the HA, thereby predisposing the allograft to HAT. In our series, the donor to recipient body weight ratio tended to be lower among the patients with HAT, and the 2 allografts which underwent pre-transplant right lobectomy resulted in a small graft for recipient size, and both went on to develop HAT. This mismatch of the donor and recipient liver size, i.e, the placement of a small liver to a recipient with a larger native liver may be an important factor in the development of HAT in pediatric patients.

The cold ischemia time was the only predictive clinical parameter for the development of HAT. This suggests that intimal damage or an increase in HA resistance from cellular swelling during cold storage (10, 11) is a factor for the development of HAT. Since the incidence of HAT seems to be lower with the use of University of Wisconsin (UW) solution (12), a new preservation fluid which is effective in preventing cellular swelling (11), it is suggested that reduction of the arterial resistance of the graft may be a key factor in preventing HAT after pediatric OLTx.

In vascular surgery, the presence of a critical flow for the development of graft thrombosis, such as 100 ml/min for femoro-popliteal bypass (13) and 50 ml/min for coronary artery bypass (14) has been reported. Although such a critical flow was not determined in adults by Klintmalm et al. (7), the fact that all 4 pediatric allografts with a HA flow of less than 60 ml/h developed HAT and that none of the other grafts studied developed HAT seems to indicate the presence of such a critically limiting flow in the allograft HA in children weighing less than 15 kg.

Rejection has been known to predispose liver allografts to the development of HAT, by creating high resistance and low flow through the HA (1, 2). In this study, it was only Case 6 of the HAT group (Table 1) in whom rejection in combination with the cessation of anticoagulation was thought to have precipitated the development of HAT.

As to postoperative anticoagulation therapy, this study did not demonstrate any significant difference between the patients with and without HAT. Our recent investigation of pediatric OLTx with the use of multivariate analysis in 47 patients, however, identified that the postoperative anticoagulation treatment was the only independent variable associated with HAT (15). We therefore continue to use current anticoagulation regimen following pediatric OLTx.

The electromagnetic flowmeter has been proven to be the most reliable method for direct measurement of HA and PV blood flow (16). It is also safe, easy to apply and gives real-time flow readings. Our data suggest that in pediatric OLTx, especially in those who weigh less than 15 kg, blood flow measurements may be a useful predictor of HAT and may be considered an important adjunct in the overall technical management of these cases.

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