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Functional Analysis of Grafts from Living Donors

Implications for the Treatment of Older Recipients

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Objective
Living-related liver transplantation (LRLT) has established efficacy in children. In a larger recipient, LRLT requires the use of a small graft because of limits on the donor hepatectomy.

Summary Background Data
The minimum graft weight required for successful transplantation has not been well established, although a characteristic pattern of graft dysfunction has been observed in our patients who receive small grafts. The authors present a clinicopathologic study of small liver grafts obtained from living donors.

Methods
Clinical and histologic data were reviewed for 25 patients receiving LRLT. In five older recipients (small group), the graft represented 50% or less of expected liver weight, whereas in 20 others (large group), the graft represented at least 60% of expected liver weight. A retrospective analysis of graft function was conducted by analyzing clinical parameters and histology.

Results
In the small group, 2 of 5 grafts (40%) were lost due to poor function, leading to one patient death (20% mortality), whereas in the large group, 2 of 20 grafts (10%) were lost due to arterial thrombosis without patient mortality. Early ischemic damage related to transplant was comparable with aspartate aminotransferase 203 ± 23 (small group) and 290 ± 120 (large group) at 24 hours (p = not significant). Early function was significantly decreased in the small group, with prothrombin time 18.2 ± 2.2 seconds *versus* 14.8 ± 1.6 seconds (large group) on day 3 ($p = 0.034$). All small group patients developed cholestasis with significantly increased total bilirubin levels at day 7 (16 ± 5.2 mg% *vs.* 3.7 ± 2.7 mg%; $p = 0.021$) and day 14 (12.0 ± 7.4 *vs.* 1.8 ± 0.7; $p = 0.021$) compared with the large group. Protocol biopsies in the small group revealed a diffuse ischemic pattern with cellular ballooning on day 7, which progressed to cholestasis in subsequent biopsies. Large group biopsies showed minimal ischemic changes. Three small group patients recovered with normal liver function by 12 weeks.

Conclusions
Clinical recovery after a small-for-size transplant is characterized by significant functional impairment associated with paradoxical histologic changes typical of ischemia. These changes apparently are due to graft injury, which can only be the result of small graft size. These findings have significant implications for the extension of LRLT to adults.

The recent evolution of liver transplantation has been marked by an increasing scarcity of donor organs that fundamentally limits access to this life-saving therapy. Currently, nearly 5000 patients are listed for transplantation in the United States, with an expected supply of 3500 donor organs.[1] This crisis has generated controversies in patient selection[2] and driven research in several areas, including xenografting[3] and surgical reduction of livers to create new grafts, including the splitting of livers to create two grafts and live-donor liver transplantation.[4] Living-related liver transplantation (LRLT) has established efficacy in the treatment of children and more than 800 cases have been reported to the International Registry in Hamburg (C. E. Broelsch, personal communication, January 1996). These modalities essentially have eliminated mortality on the waiting list for children. Unfortunately, many barriers limit the extension of LRLT to adults, and few successes have been reported. In fact, the disparity between supply and demand for the adult recipient is worsening and represents a major crisis in the transplant community.

The major limitation of LRLT for adult recipients is that the amount of liver that can be removed safely from the living donor is too small to function as a graft for most recipients. Several reports of LRLT have included a few adult subjects, but a high failure rate has been observed. Recently, Makuuchi has reported a series of 14 adults with a single failure, suggesting the feasibility of this approach (M. Makuuchi, personal communication, January 1996).[5] These well-selected patients tended to be small, with preserved synthetic function in the recipients, and total left hepatectomy in the donor was required to obtain the largest possible graft. In a single case in the Kyoto series, a right hepatectomy was performed in the living donor.[6] These parameters clearly limit the applicability of LRLT to a small subgroup of adult recipients.

In this retrospective study, we conducted a clinicopathologic analysis of postoperative graft function in 25 recipients of LRLT to define the parameters limiting the use of LRLT in larger recipients. We hypothesized that graft size predictably is correlated to function in the recipient. This hypothesis was supported strongly by the data in this series, suggesting that graft size is a key factor is the assessment of candidacy for LRLT and that alternative strategies will be required for the extension of LRLT to the adult population.

METHODS

Patient Population

Recipients

Twenty-four patients received LRLT in our medical center between November 1992 and April 1996. One additional patient transplanted by the principal author in another center in November 1991 was included because he was the first case of LRLT using a small graft in our experience. Selected clinical and laboratory data describing the patients studied are presented in Table 1. A spectrum of acute and chronic liver disease is represented, although biliary atresia is predominant. Although most of the patients were small children (median age 1.5 years), the range included patients between 3 months to 59 years of age. Most of the patients were elective (UNOS status III), although six were hospitalized at the time of

Table 1. PREOPERATIVE DATA

Diagnosis			
Biliary atresia	14		
Alpha-1-antitrypsin deficiency	3		
Fulminant hepatic failure	2		
Crigler-Najjar	1		
Urea cycle defect	1		
Neonatal hepatitis	1		
Alagille	1		
Hepatoblastoma	1		
Cryptogenic cirrhosis	1		
Age (yrs)			
Mean	5.9 ± 12.0		
Median	1.5		
Range	3–59		
Weight (kg)			
Mean	15.5 ± 12.7		
Median	10.6		
Range	5.5–51		
UNOS status			
1	2 (8%)		
2	4 (16%)		
3	19 (76%)		
Clinical status			
Ascites	14 (56%)		
Previous upper gastrointestinal bleed	7 (28%)		
Previous encephalopathy	7 (28%)		
Laboratory data			
Assay	**Mean**	**Median**	**Range**
Total bilirubin (mg/dL)	14.2 ± 12.9	7.7	0.8-51
Prothrombin time (sec)	15.0 ± 2.9	13.8	12–60
Aspartate aminotransferase	230 ± 225	174	47–4500

UNOS = United Network for Organ Sharing.

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orthotopic liver transplantation, two of whom were critically ill (UNOS status I). Other clinical and laboratory parameters were typical of a population of end-stage liver patients.

Donors

The donor evaluation has been described elsewhere.[7] All patients selected as donors were healthy, free of chronic medical illness, and ranged in age from 19 to 47 years. All were biological relatives, including 11 fathers, 11 mothers, 2 aunts, and 1 son. Computed tomographic liver volume measurements were not used to exclude donor candidacy because the method currently is being validated in our center. Furthermore, in our efforts to expand the application of LRLT, a wide range of liver volumes were used for transplantation.

Surgical Techniques

Surgical techniques have been described elsewhere.[4,8] The donor operation is composed of a dissection of the vascular and biliary pedicles followed by transection of the liver. The ultrasound dissector has been used in all recent cases (n = 17), and no hepatic clamping was performed. The bile duct is identified by peripheral transection at the base of the round ligament, and no cholangiography is performed. The left lateral portion of the liver (segments II and III[9]) was used in all but two cases, in which segments II, III, and IV were used. Hepatic venous implantation was used with the triangulation method to locate the grafts in the orthotopic position and to optimize the outflow orifice.[10,11] Cryopreserved vein grafts were used to extend the portal vein in the earliest 8 cases, whereas in 17, direct anastomosis was accomplished without difficulty. Microvascular arterial reconstruction was performed in these 17 cases according to the Kyoto technique.[12] When the graft was small, malpositioning was avoided by plication of the right hemidiaphragm to obliterate the large fossa normally occupied by the right lobe of the liver, thereby keeping the liver central and avoiding twisting of the vena cava.

Medical Management

Sequential induction therapy using antithymocyte globulin (Atgam, Upjohn, Kalamazoo, MI) was used followed by cyclosporine, azathioprine, and prednisone as the baseline regimen. Five patients have required conversion to tacrolimus for either resistant rejection (n = 3) or improved absorption of immunosuppression. In the last 17 cases, cyclosporine (Neoral, Sandoz Pharmaceutical Corp., East Hanover, NJ) and mycophenolate mofetil (Cellcept, Hoffman-LaRoche, Palo Alto, CA) have been used as standard induction. Protocol biopsies are performed in our center on days 7 and 14. If rejection is present, weekly biopsies are continued until two successive biopsy results show no evidence of rejection. Immunosuppression and all other medical management do not differ between recipients of cadaveric or living-donor transplants.

Table 2. OPERATIVE DATA

Parameter	Mean	Median	Range
Donor OR time (min)	293 ± 51	286	220–391
Donor blood loss (mL)	1031 ± 1060	600	200–4500
Recipient OR time (min)	433 ± 72	430	270–565
Recipient blood loss (mL)	2184 ± 5761	800	200–30000
Cross-clamp time (min)	48 ± 11	51	15–62
Ischemic time (min)	239 ± 62	343	155–613

OR = operating room.

Study Design and Data Collection

Data were collected from the University of California-San Francisco liver transplant database and review of the medical records. Selected preoperative (Table 1) and perioperative data (Table 2 and 3) were collected and analyzed based on the hypothesis that a relationship could be determined between one or more of these variables and outcome variables representing the rapidity at which graft function normalized after transplantation (Table 4). Graft function was assessed daily by standard liver function tests and was expressed as the number of days until a target value was observed (aspartate aminotransferase < 150 international units/L, total bilirubin < 5.0 mg/dL, and prothrombin time < 14 seconds). In the case of a very small graft that never functioned and was replaced on day 7, a value of 62 days was arbitrarily assigned because the true interval to normal function was infinity. Sixty-two was chosen because it was the longest interval observed among the other patients.

The equation proposed by Urata et al.[12] for the prediction of the liver volume for a healthy person was used to estimate the size of liver that was ideal for each recipient. An actual liver volume was measured using saline displacement after the graft was removed in 21 of 25 cases. The graft volume ratio was the actual volume of the graft divided by the predicted liver volume for each recipient.

Pathologic Analysis

All biopsies were reviewed by a blinded observer and scored for selected parameters reflecting injury, (cell dropout, ballooning, steatosis, cholestasis) or regeneration (mitoses, double-cell plates, multinucleate cells, small cell changes, and pseudogland formation).

Table 3. LIVER GRAFT DESCRIPTION

	Mean	Median	Range
Liver weight*	286 ± 123	250	150–650
Predicted recipient liver weight†	357 ± 267	235	149–1019
Liver weight ratio‡	1.06 ± 0.7	0.97	0.23–3.51
Predicted donor liver weight†	1284 ± 138	1249	1038–1699
Donor graft fraction§	0.21 ± 0.08	0.18	0.13–0.49

* Measured by graft volume displacement.
† Calculated from equation after Urata.[14]
‡ Actual weight/predicted recipient liver weight.
§ Actual weight of segment II, III graft/predicted donor liver weight.

Data Analysis

All data were analyzed as continuous variables. Simple linear regression was used with calculation of the F statistic to determine the probability of correlation. A p value < 0.05 was considered significant. A correlation matrix was constructed using variables with significant correlation to the outcome variables. Multivariate analysis was not attempted because of the small sample size.

RESULTS

Patient and Graft Survival

Overall, 23 children (<15 years) and 2 adults were included. All children are alive between 1 and 50 months post-transplantation. One of two adults is alive 22 months after transplantation. Four grafts were lost at 7 days (primary nonfunction), 12 days (arterial thrombosis), 62 days (sepsis), and 18 months (sepsis, arterial thrombosis). Three children are alive with retransplants from cadavers.

Operative Data

Operative data are presented in Table 2. Donor surgery lasted between 220 and 391 minutes, with a median blood loss of 600 mL. It is our surgical impression that large male donors with thick livers require more time with greater blood loss during parenchymal transection. The only patient who required heterologous transfusion (4 units) had a segment II and III of 400 g. Recipient surgical times were typical for liver recipients. An extremely high blood loss occurred in the adult recipient who eventually died of surgical complications. She had advanced cryptogenic cirrhosis with ascites and extensive previous surgery.

Total ischemic time ranged from 155 to 613 minutes (median 340 minutes). The clamp time in the recipient was between 28 and 62 minutes. Of this time, roughly 30 minutes is required to complete the anastomoses, whereas the remainder is required to prepare the recipient vena cava, closing all the small venous orifices.

Liver Grafts

Of the 25 grafts (Table 3), 23 comprised segment II and III whereas 2 were full left lobes (segments II, III, and IV). Liver volume displacements ranged from 150 to 650 mL, with a median of 250 mL. The two left lobes were markedly different is size; one, from a small female, was only 200 mL, whereas the other, from a large male donor, was 650 mL. Using the Urata equation, we estimated the total liver weight of each donor.[12] Donor livers were between 1038 g and 1699 g, with a median of 1249 g. Among the left lateral segment grafts (II and III), when the actual weight of the resected segment was divided by the estimated weight of the donor's liver, the left lateral segment made up a median 18% of the donor's liver. However, because of variations in morphology, this portion varied between 13% and 49%.

Similarly, using the Urata equation, we estimated the total liver weight of each recipient. The weight of the ex-

Table 4. FUNCTIONAL ANALYSIS

	Prothrombin Time		Total Bilirubin	
	r	p	r	p
Correlation of operative variables with postoperative graft function				
Cross-clamp	0.053	NS	0.029	NS
Donor OR time	0.087	NS	0.068	NS
Donor blood loss	0.491	0.015	0.411	0.045
Recipient OR time	0.225	NS	0.292	NS
Recipient blood loss	0.541	0.005	0.504	0.01
Ischemic time	0.035	NS	0.014	NS
Correlation of clinical variables with postoperative graft function				
Age	0.800	0.0001	0.789	0.0001
Weight	0.772	0.0001	0.874	0.0001
UNOS	0.043	NS	0.065	NS
Ascites	0.036	NS	0.049	NS
UGIB	0.183	NS	0.059	NS
Encephalopathy	0.170	NS	0.117	NS
AST	0.128	NS	0.159	NS
PT	0.031	NS	0.070	NS
Total bilirubin	0.311	NS	0.213	NS
Graft parameters				
Recipient liver weight	0.012	NS	0.090	NS
Small graft*	0.650	0.0004	0.788	0.0001
Liver graft ratio†	0.451	0.0402	0.470	0.0318

OR = operating room; NS = not significant; UNOS = United Network for Organ Sharing; UGIB = upper gastrointestinal bleed; AST = aspartate aminotransferase; PT = prothrombin time.
*Graft < 50% of expected mass.
†Graft weight/expected liver weight.

Table 5. SUMMARY OF HISTOLOGIC FINDINGS

	Rejection	Ischemia	Cholestasis	Mitosis	Regeneration
Small (n = 5)	0 (0%)	5 (100%)	5 (100%)	1 (20%)	5 (100%)
Large (n = 20)	9 (45%)	8 (40%)	8 (40%)	15 (75%)	9 (45%)

plant was not considered because the goal was to compare the amount of liver transplanted with the weight of the liver needed by a healthy recipient. Therefore, the liver weight ratio, the actual weight of the graft divided by the expected liver weight for each recipient ranged from 0.23 to 3.51. For the 21 patients for whom exact graft weights were available, 12 received grafts larger than the expected liver weight (ratio > 1) whereas 5 received grafts that were clearly small for size (between 23% and 44% of expected liver size; Fig. 1).

Postoperative Graft Function

Of the 25 grafts, 21 are currently functioning up to 50 months after orthotopic liver transplantation. Using the parameters of early functional recovery defined in this study, prothrombin time entered the normal range (<14 seconds) within 8 days or less in 21 of 25 (84%) cases, whereas total bilirubin fell below 5 mg/dL within 8 days in 19 of 25 (76%). All five patients with delayed recovery of prothrombin time had small grafts with weight ratios below 0.5. Four of these five patients were encephalopathic in the first week after transplant. Rejection was diagnosed by biopsy in six patients, none of whom experienced delayed restoration of synthetic function. Surgical complications occurred during the first hospitalization in five patients (hemoperitoneum, n = 1; arterial thrombosis, n = 1; primary nonfunction, n = 1; biliary dehiscence n = 2).

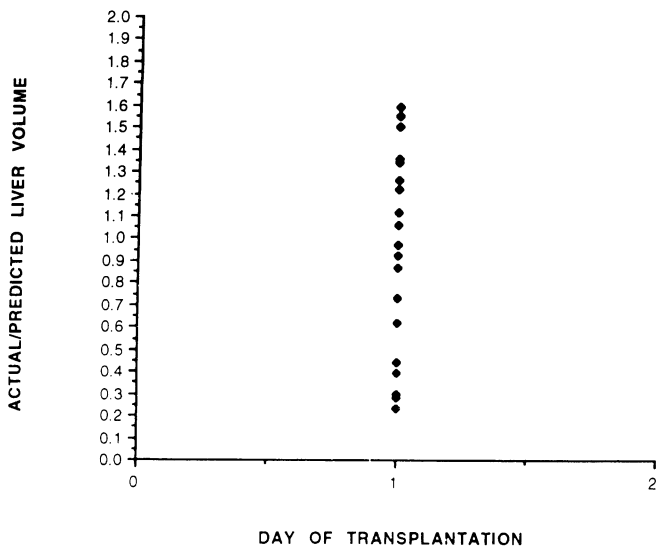

Figure 1. Scattergram of graft volume fraction (actual liver size/predicted normal liver size). Livers used in this series ranged from 0.23 to 3.51.

Regression Analysis

Regression analysis was performed to detect associations between selected clinical variables and functional outcomes after transplantation (Table 4). Three types of data were considered: preoperative clinical and laboratory data, graft related data, and operative findings. The presence or absence of rejection also was considered. Three separate outcome variables were considered, aspartate aminotransferase reflecting graft injury, prothrombin time reflecting immediate synthetic function, and total bilirubin reflecting overall function. The days required for normalization of these variables are plotted in Figure 2.

None of the variables considered in the analysis correlated significantly with aspartate aminotransferase. In contrast, age, weight, the presence of a small graft (graft ratio < 0.5), graft ratio, and both donor and recipient blood loss all correlated with normalization of total bilirubin and prothrombin time (Fig. 3). Multivariate analysis was not performed because n = 25 was small. A correlation matrix was constructed demonstrating high intercorrelation between age, weight, small graft, and graft ratio, which is evident because the larger the recipient, the smaller the relative size of the graft. In contrast, donor and recipient blood loss seemed to contribute independently to the functional outcome.

Histologic Analysis

A summary of biopsies obtained on days 7 and 14 is presented in Table 5. These biopsies were scored for the principal findings associated with postoperative graft injury focusing on hepatocellular cholestasis, ischemic findings, and changes associated with regeneration such as mitosis, small cell changes, pseudogland formation, double-cell plates, and the presence of multinucleated cells. When patients who received small grafts (volume ratio < 0.5) were compared with recipients of larger grafts, consistent differences were observed. All recipients of small grafts demonstrated early changes associ-

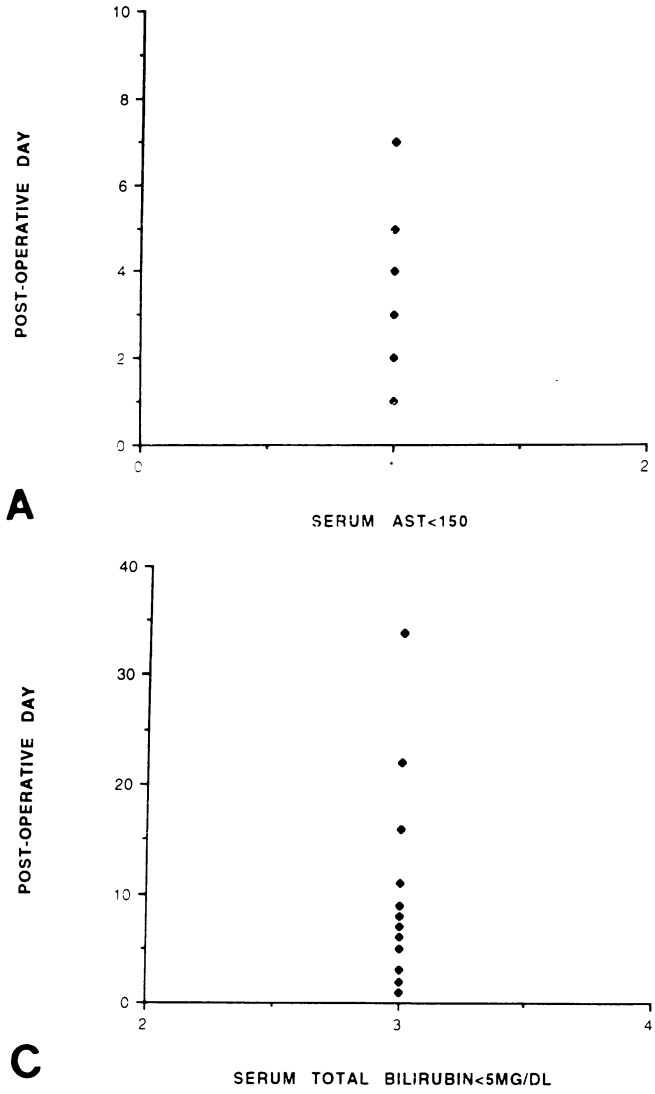

Figure 2. Scattergram of postoperative laboratory tests. The number of days required to return to target levels for aspartate aminotransferase (<150 (A), prothrombin time (<14 seconds (B), and total bilirubin (<5 mg/dL (C).

ated with poor function and cholestasis (Fig. 3). In contrast, 8 of 20 patients with larger grafts exhibited these changes. Rejection was present in at least one biopsy in nine patients; it was mild in seven and moderate in two. Interestingly, none of the patients with small grafts exhibited signs of rejection.

DISCUSSION

In this study, the relationship between graft size and function is clearly defined. Older recipients of LRLT consistently experienced delay in the restoration of liver function characterized by early coagulopathy and encephalopathy, culminating in a prolonged period of cholestasis. Although this functional impairment was observed to recover in most cases, one child who received a graft accounting for 23% of predicted liver mass never functioned and was replaced on day 7. The analysis of a series of living-donor liver grafts permits the elimination of variables such as preservation time and the great variety of insults that affect the functional outcome of cadaveric grafts.[13] Although the predictive power of these data is limited by the small size of the series, a clearly defined pattern of liver dysfunction was observed when the graft represented less than 50% of the expected liver volume for the recipient. These findings indicate that widespread extension of living donation to adult liver recipients will be limited by the ability to obtain a graft of sufficient volume to maintain life.

Although the clinical syndrome of liver dysfunction is well characterized in this series, we are unable to draw firm conclusions about the pathophysiology. Several features have been associated with poor functional outcome of cadaveric grafts, including steatosis in the donor.[13] The grafts in this series, coming from living donors, all had normal liver tissue at baseline and were subjected to a relatively narrow range of short preservation times. After reperfusion, the small livers were firm, suggesting that

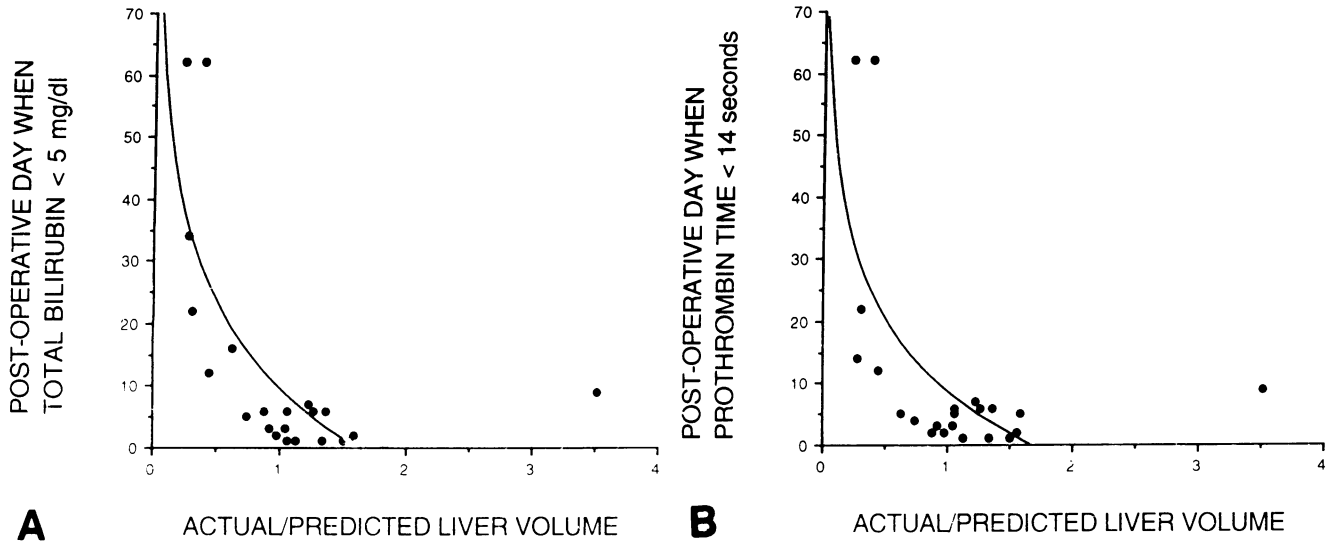

Figure 3. Correlation curves of graft cholestasis: (A) bilirubin and (B) function (prothrombin time) to living-related liver transplantation graft fraction.

they were exposed to an excessive portal perfusion. Several lines of experimental data suggest that hyperperfusion of the liver is detrimental and improved results have been observed with portal decompression of small liver grafts.[14] The injury sustained by the small graft may be comparable to events observed after massive hepatectomy when a small remnant is required to maintain life. In addition to high blood flow, the small remnant is exposed to increased amounts of gut-derived endotoxin and substrates, including fatty acids that may overwhelm the metabolic capacity of the compromised graft. Paradoxically, the liver biopsies of the small grafts initially were interpreted as demonstrating "preservation injury" a syndrome characterized by hepatocyte ballooning and steatosis, centrilobular necrosis, and parenchymal cholestasis. This injury occurred in the face of excessive blood flow and more likely reflects a nonspecific pattern of injury rather than one specifically associated with ischemia. The sequential pattern of recovery documented histologically in Figure 4 demonstrates that this process is reversible.

The recovery of function observed in several patients is compatible with the ability of the small graft to regenerate in the foreign host. This process has been well documented in several experimental models of transplantation[15] and occurs clinically on occasions when pediatric donors have been used for adults.[16] Despite the ability to regenerate, the small liver is vulnerable to other insults, however, and we presume that recipients of small grafts are at risk for other complications during the recovery period. Even with larger numbers of cases, it may not be possible to define with certainty the safe lower limit of graft size that could be used for transplantation because the clinical outcome depends on both the available parenchyma and factors that vary between recipients. The clinical sequence of recovery was consistent because encephalopathy resolved over the first several days, followed by the improvement of synthetic function reflected by the prothrombin time. In contrast, cholestasis was much slower to resolve, consistent with other forms of liver injury. We did not perform sequential scans to objectively document the restoration in liver mass, although on clinical assessment, graft size returned to normal within 3 months. This impression is consistent with previous data, in which mass restoration was documented with volumetric computed tomography scans.[17]

This series included five patients with very large grafts who required temporary enlargement of the abdomen with prosthetic patches to avoid abdominal compression on closure. Clinically, these livers decrease rapidly in size, and abdominal closure usually can be completed within 1 week. The histologic findings of these livers are usually nonspecific and function is excellent. Despite these empirical observations, little is known about the downregulation of excessive liver size. Obviously, in contrast to conditions in which the liver is injured or made smaller by trauma or disease, no natural events lead to an excess of liver. It is possible to suppose that apoptosis plays a role in the decrease of liver size, and there is experimental support for this concept.[18] The study of patients receiving oversized livers should be helpful in clarifying liver mass regulation.

Review of the factors associated with delayed function of the grafts clearly implicated small size as the dominant factor contributing to impaired postoperative function. R values for both age and weight actually were higher than graft volume, but we account for this by the fact that we lacked graft weight measurements in four cases.

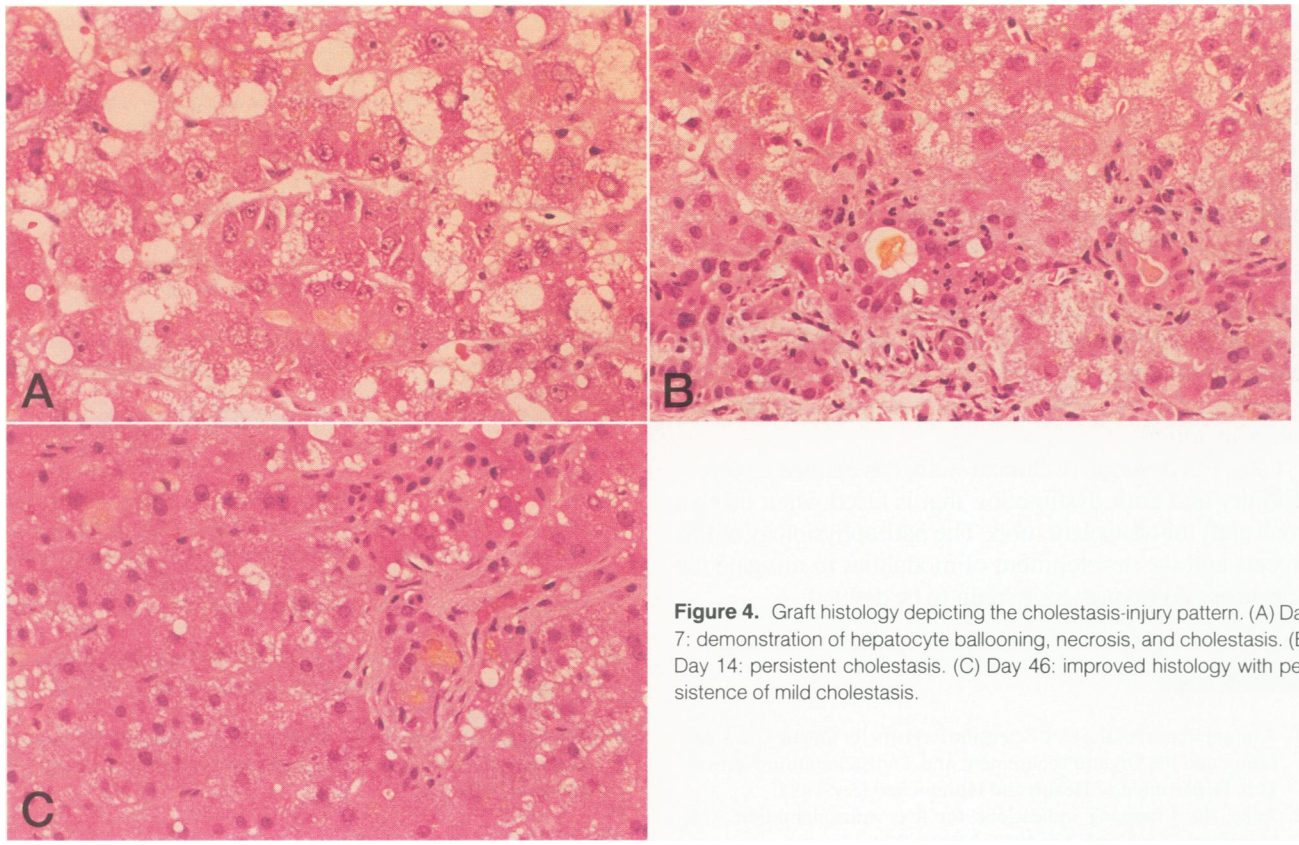

Figure 4. Graft histology depicting the cholestasis-injury pattern. (A) Day 7: demonstration of hepatocyte ballooning, necrosis, and cholestasis. (B) Day 14: persistent cholestasis. (C) Day 46: improved histology with persistence of mild cholestasis.

It is unlikely that age and weight contribute independently to poor function because comparable recipients of size-appropriate cadaveric grafts demonstrate excellent graft function. Both donor and recipient blood loss appeared as factors that might be correlated independently with functional outcome. This is reasonable because blood loss could be a marker for the severity of the surgical injury. Makuuchi has proposed that the condition of the recipient is an important variable in the outcome of small grafts for transplantation of adults (M. Makuuchi, personal communication, January 1996).[5] In our analysis, we were unable to detect a correlation between preoperative liver function and postoperative function, although a type 2 error can not be excluded.

Although the occurrence of rejection was not a primary outcome variable in this study, there is reason to postulate a relationship between regeneration and rejection. The primary hypothesis is that the regenerating liver is an altered immunologic target. Several studies in rats have demonstrated accelerated rejection of regenerating allografts in rats.[19] Despite these observations, no rejection occurred in the recipients of small grafts in this series. In addition to being altered as a target, the small liver should be less able to withstand the loss of hepatocytes caused by immune attack because of its decreased parenchymal reserve. An alternative hypothesis is that the regenerating liver expresses a decreased amount of antigenic targets because of the relative dedifferentiation that occurs during regeneration.

Regardless of the mechanism of liver dysfunction in the older recipients of living-related liver grafts, use of this technology has been limited. In contrast to the extremely high success rates reported for small children by our group and others with survival rates exceeding 90%, few adults have been grafted successfully by this technique.[4] Our data suggest that patients receiving less than 50% of liver mass will experience transient function impairment. In the largest series of adults reported to date (n = 12), Kawasaki emphasized preserved liver function in the recipient and favorable donor-recipient size match as important variables in patient selection (M. Makuuchi, personal communication, January 1996).[5] Fan has successfully grafted a patient with a liver from a spousal donor accounting for approximately 25% of expected liver mass.[20] Our failure to observe life-sustaining function in a graft of 23% size suggests that the lower limit of graft size is in this range.

Regardless of the absolute limits of graft size that can be used, the expansion of living donation to adults will require a change in tactics. Pharmacologic protection of the liver and enhancement of regeneration, as well as the development of effective liver-assist devices, could permit the use

of small livers as standard orthotopic replacements. Alternatively, the extent of resection could be increased in the donor. This proposal has extremely troubling ethical implications because the risk/benefit analysis favoring the introduction of this therapy was predicated on the removal of a relatively small amount of liver from the donor.[21] The most promising modification is the use of the living donor liver as an auxiliary graft, exploiting both the regenerative potential of the graft and the residual function of the remnant liver. This approach was pioneered by Terpstra and Broelsch using portions of cadaveric livers.[22–24] We currently are planning the use of auxiliary livers from living donors for the treatment of both acute and chronic liver failure in adults.

Thus, this descriptive clinical study has defined a pattern of injury and graft dysfunction that is faced when using a small graft for transplantation. The pathophysiology of this process and the development of modalities to mitigate the deleterious consequences remain to be defined.

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Discussion

DR. HENRI BISMUTH (Villejuif, France): I had great pleasure in reading this paper, for really it brings some clarity to the difficult issue of using small grafts in liver transplantation. Dr. Emond says that early function of the graft significantly decreases if the graft is smaller than 50% of the expected volume. This figure is much less than the hepatic resection in patients with nontransplanted livers. In fact, we can remove 75% to 80% of the normal liver without risk for the patient. How does one explain this difference? Is there some degree of portal hypertension, for instance, and because of the decreased resistance through the small graft the portal flow is diverted through the collateral circulation developed before transplantation? I would like to ask Dr. Emond if the portal pressure was measured during the transplantation.

Now, in living-related liver transplantation, the graft coming from the donor is surely the best; there is less ischemic damage and also the quality of the parenchyma is usually very good. In split-liver transplantation, which is likely to become more popular because of the increasing disparity between cadaver organ availability and demand, the quality of the graft usually is not so good; sometimes there is some degree of steatosis in the donor, the manipulation of the graft is more important, and the overall duration of ischemia is longer. I would like to ask Dr. Emond what he thinks is the minimal size of the graft we may use in split-liver transplantation.

DR. ACHILLES A. DEMETRIOU (Los Angeles, California): I would like to congratulate the authors for a very well done clin-