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Re-use of a liver graft and multi-organ procurement from a liver transplant patient

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Dear Editors: Re-use of a liver graft with satisfactory results has been reported previously [1, 2, 3, 4]. Liver procurement from the transplant patient was associated with kidney procurement in one case [2] and with cardiac procurement in another (J. Lerut et al., unpublished observation). Herein we report the first case of heart-and-lung procurement together with re-use of a freshly transplanted liver from a young brain-dead woman following liver transplantation for acetaminophen-induced acute hepatic failure.

The initial liver recipient was a 21-year-old woman with blood group 0 who was referred to our intensive care unit after ingestion of 16 g of acetaminophen. Initially, N-acetyl cysteine treatment (150 mg/kg per day) was instituted at 17 h after evidence of intoxication had been established by an acetaminophen blood level of 688 mmol/l, ASAT of 855 IU/l, and ALAT of 427 IU/l. Upon admission, 34 h after ingestion, the patient had acute hepatic failure without encephalopathy, with ASAT at 2390 IU/l, ALAT at 837 IU/l, and a factor V of 29%. The clinical course was stable during the following 12 h, without neurological symptoms, but with worsening liver function: ASAT was at 5310 IU/l, ALAT at 2277 IU/l, and factor V was 14%. Twelve hours later she showed sleepiness, the electroencephalogram (EEG) was stage 1, and ASAT, ALAT, and factor V were 5500 IU/l, 3300 IU/l, and below 10%, respectively. Neurological deterioration (flapping and confusion) with EEG stage III led us to put her on the waiting list as highly urgent patient about 60 h after ingestion. Hemodynamic and renal status were normal at that time. Twenty hours later, an orthotopic liver transplantation was possible.

The initial donor was a 48-year-old man with blood group 0, brain-dead due to cerebral stroke. Brain death was confirmed by clinical signs and two EEGs registered at 4-h intervals as legally required in France. The hemodynamic state was stable with 1.6 mg/h of noradrenaline. Serology for hepatitis B and C was negative, and liver tests were in the normal range (bilirubin 13 mg/l, glutamyl transferase 16 IU/l, ALAT 33 IU/l, and ASAT 15 IU/l). The heart was not proposed for procurement because of unfavorable echocardiography data. After verification of non-opposition to organ donation, harvesting was begun. The liver parenchyma appeared normal in consistency and color after laparotomy in the donor. Liver, pancreas, and both kidneys were retrieved after perfusion with 4 l of UW solution via the aorta and 1.5 l via the portal vein.

In the immediate pre-transplantation period, the first recipient

showed altered renal function with oliguria and an increase in serum creatinine (20 μmol/l). In the operating room, pre-incision EEG was stage IVa and pupils were normal. Hemodynamic monitoring was performed by means of a Swan-Ganz catheter and arterial blood pressure device. Liver transplantation was performed with a lateral vena cava anastomosis without temporary portocaval shunt. Cold ischemic time and the anhepatic phase were 430 and 65 min, respectively. Blood loss was 600 cc, comprising 250 cc for splanchnic purge. Fluid replacement necessitated 6 units of packed red blood cells and 8 units of serum albumin diluted at 4% concentration. No fresh frozen plasma was used as previously described in our protocol [5]. Despite persistent oliguria, hyperkalemia or acidosis were not noted, whereupon we did not commence hemodialysis. At the end of transplantation, the recipient was maintained under mechanically assisted ventilation to reach PCO_2 (about 30 mmHg) in order to minimize cerebral edema. PO_2 was about 280 mmHg with FIO_2 at 50%. Blood pressure was above 170/80 mmHg, mean pulmonary arterial pressure was 18 mmHg, and cardiac frequency about 115/min. Pupillary monitoring at the end of the third phase of transplantation showed a tendency towards mydriasis. Anesthetic drugs with myotic effects (atropine and adrenaline) were not used during transplantation. Immediate postoperative biological tests, listed in Table 1, showed good initial liver function, but persisting oliguria, unless furosemide and dopamine (3 μg/kg per min) were administered. The cross-match was negative and immunosuppression was started with prednisolone, anti-IL2 monoclonal antibody (Zenapax, Roche, Rueil-Malmaison, France), and mycophenolate mofetil (Roche, Rueil-Malmaison, France). The immediate clinical course was complicated by hypertension and tachycardia, and then by complete mydriasis 6 h after unclamping. Eight hours after these neurovegetative disturbances, a first postoperative EEG showed deteriorated brain function. A second EEG confirmed brain death 18 h after unclamping. Following emotional, ethical, and technical discussions within the team, informed consent for organ donation was obtained from the family of this young woman.

As a secondary organ donor, the first liver recipient was managed by standard clinical and biological monitoring. In accordance with the legal requirement of determination of brain death, irreversible brain damage was confirmed by an arteriogram of the four cerebral vessels, which showed no intracranial flow. Viral tests and liver tests were normal, as given in Table 1. Cardiac and pulmonary parameters were strictly normal, authorizing the proposal of an associated cardiopulmonary procurement. Upon laparotomy, the liver appeared normal in terms of color and consistency. Organ retrieval was performed 47 h after first unclamping the transplanted liver, with aortic and portal perfusion of 4l and 1.5l of UW solution, respectively, at the abdominal level and 2l of Celsior solution at the thoracic level.

The recipient of the heart-and-lung graft was a 49-year-old man with bronchiolitis obliterans. Cold ischemic time was 255 min. The cardiopulmonary procedure and postoperative course were uneventful. The recipient had an episode of moderate rejection at 3 months and was well 11 months later.

The second liver recipient was a 61-year-old woman who had hepatitis C cirrhosis, Child-Pugh score 11, with esophageal varices and refractory ascites. Liver transplantation was performed according to the same protocol as for the first transplantation; cold ischemic time was 310 min and the anhepatic phase 90 min. The liver transplant procedure and immediate postoperative course were uneventful. The cross-match was negative and initial immunosuppression consisted of prednisolone, cyclosporine (Neoral, Novartis, Rueil–Malmaison, France), and mycophenolate mofetil (Roche, Rueil-Malmaison, France). Liver function became favorable rapidly, with a rather low peak of transaminases and a fast increase in factor V level (Table 1). Post-reperfusion liver biopsy showed a slight ferric overload inside Kupffer cells and hepatocytes. No episodes of rejection occurred, and at 2 months, reinfestation by hepatitis C virus was detected in the serum by means of PCR and con-

Table 1 Kinetics of biochemical parameters of liver graft (*ALAT* alanine aminotransferase, *ASAT* aspartate aminotransferase, GGT γ-glutamyl transferase, *AP* alkaline phosphatase)

	Liver tests in the first recipient					Liver tests in the second recipient				
	12 h before Tx	After 7 h	After 16 h	After 33 h	After 40 h	After 2 h	Day 1	Day 7	Day 14	Day 24
Bilirubin (mg/dl)	70	37	26	17	17	40	22	21	11	8
ALAT (IU/l)	1880	803	493	270	250	325	149	25	27	29
ASAT (IU/l)	2540	1377	1358	1105	1050	304	279	98	64	47
GGT/AP (IU/l)	28/166	59/146	55/161	43/151	41/176	47/42	84/32	255/164	213/79	226/4
Factor V	< 10%	13%	36%	57%	65%	11%	47%	122%	101%	100%

Table 2 Source and outcome of reported cases of re-used liver graft (*PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis, *RTX* re-transplantation, *ND* not determined, *HCV* hepatitis C virus)

Cases	1st donor	1st recipient/1st transplantation				Time span[a]	2nd recipient /2nd transplantation				Survival (months)
	Age (years)	Age (years)	Etiology	Cold ischemia (min)	ASAT/ALAT (IU/l)[b]	(hours)	Age (years)	Etiology	Cold ischemia (min)	ASAT/ALAT (IU/l)[b]	
1 [1]	40	57	PBC	112	< 250	22	29	RTX	100	< 250	dead, 48
2 [1]	22	54	PSC	260	420/480	43	32	RTX	90	150/400	dead, 4
3 [1]	23	51	RTX	115	500/300	45	56	HCV	60	450/250	25
4 [2]	24	24	RTX	ND	353/159	120	52	Alcohol	360	45/46	6
5 [3]	65	55	Alcohol	314	ND/720	ND	58	HCV	660	ND/866	ND
6 [4]	ND	21	ND	ND	ND	24	ND	ND	ND	ND	24
7[c]	15	47	Paracetamol	569	400/500	29	53	HCV	659	700/300	ND
Our case	48	21	Paracetamol	430	1377/803	47	61	HCV	310	304/325	9

[a]Between 1st and 2nd transplantation (h)
[b]Peak, several values are from figures in the corresponding report
[c]J. Lerut et al., unpublished observation

firmed by liver biopsy. The recipient was well 11 months after transplantation.

Cerebral hemorrhage and transient edema are dreaded complications after liver transplantation for acute hepatic failure and may lead to brain death of the recipient. The re-use of a transplanted liver in such situations for a second recipient has previously been described for seven cases, once in association with kidney [2] and once in association with heart procurement (J. Lerut et al., unpublished observation) from the brain-dead liver recipient, but none of these cases comprised both heart and lung procurement. This is probably due to two factors: first, the emotional context of such a procedure focuses on the transplanted organ, and not on the others; and secondly, type and duration of peritransplantation management may alter the initial recipient's own organs. In our case, the recipient's early death led us to look beyond the abrupt failure of transplantation and to hypothesize on the potential success of a further transplantation in order not to lose the liver graft. The very brief time span between admission and brain death of the patient probably contributed to this measure. Moreover, the favorable attitude of the family towards donation led the transplant team to ask the coordinators to begin with procurement formalities. It also facilitated proposing heart and lung procurement, which was emotionally difficult and in contrast to the procurement of the liver, which the parents thought to be "not her own property and, anyway, by now no longer useful". During the debate whether or not to retrieve the liver graft, the proposal of multiorgan procurement helped the team to consider the patient solely a donor. Nine months after her death, her parents were encouraged by their knowledge of the two durable successes of transplantation of organs donated by their daughter. It is noteworthy that the liver and heart-and-lung recipients gave their in-

formed consent to these special transplantations, especially considering their age and the advanced state of their diseases.

One of the main questions here concerns the rapidity of brain death following highly urgent liver transplantation. In acetaminophen-induced liver failure, this is generally due to a quickly fatal increase in cerebral lesions, or to lack of a donor. One could argue that a 20-h period between the onset of neurological deterioration and the call for transplantation was too long and that alternative procedures should have been used, such as the MARS system or living-related transplantation. However, an extracorporeal liver support device is ineffective in reversing brain edema, given such a delay, in the case of fulminant hepatic failure [5], and a living-related procedure was not available within 20 h in this case without excessive risk to the potential donor. In general, 66% of patients in France on the waiting list as highly urgent undergo transplantation within 24 h, as was our patient. The liver graft immediately functioned correctly as confirmed by a rapid, sustained increase in factor V level, thus excluding persistent liver dysmetabolism as an explanation for brain damage. Other factors contributing to cerebral edema in the context of acute hepatic failure are hyponatremia, hypercapnia, vascular overload, and renal failure. But transplantation was possible under minimal vascular filling for two reasons: first, blood loss was low (< 600 cc); and secondly, the vena cava of the recipient could be preserved, excluding overload, as is usually needed with total clamping. The worsening of brain edema could have been due to renal failure as reported in severe acetaminophen intoxication [6]. This is why anuria precluded kidney procurement in this context. In contrast, and unlike up to 33% of very severe paracetamol poisonings [7] either due to a direct effect of paracetamol metabolites or as a result of a rise in intracranial pressure, no lung injury and no pulmonary edema could be detected and, thus, pulmonary parameters remained satisfactory to such an extent that lung procurement and transplantation could be performed, suggesting that vascular filling had been moderate. This is the first time that such lung procurement is reported, and this may be due to the particular status of our recipient and to subsequent management. In all the other reports except one [3], each initial recipient had chronic liver failure – two of them having been in very poor condition – so that the lungs of these patients may have suffered from perioperative management. Moreover, in the case of Tantawi et al. [2], procurement of the liver occurred only 5 days after transplantation, excluding lung harvesting.

It is interesting to note that all seven previous second recipients experienced a moderate peak in transaminases after transplantation. In our opinion this was due to the initial good quality of the grafts, which were mostly retrieved from young donors (aged 40, 22, 23 [1], 24 [2], and 15 [J. Lerut et al., unpublished observation]). In all cases the first postoperative peak of transaminases was low ($ASAT_{max}$ < 500 IU/l) (Table 2). In our case the donor was 48 years old and the first postoperative peak of transaminases was higher but showed a rapid decrease. In the case reported by Figueras et al. [3], the initial donor was 65 years old and the first postoperative peak of transaminases was 720 IU/l. It can also be hypothesized that the phenomenon of ischemic preconditioning occurred, as has been described for liver surgery [8]. The first transplantation may have acted as first sequence of a clamping-unclamping maneuver, making the graft tolerant to the second period of ischemia. Finally, all of these second procurements were obviously performed from immunosuppressed patients, which may have an anticytokine effect, as described in experiments meant to reduce the deleterious impact of brain death on organs to be harvested [9].

In conclusion, this report confirms that re-used liver grafts may function very well in second recipients and that, under certain circumstances, organs of the brain-dead recipient–donor including heart and lungs may be harvested, provided that perioperative management is adapted to such a situation.

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