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The Results of Transplant Livers from Selected Non-Heart-Beating Cadaver Donors

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ABSTRACT

The clinical experience following transplantation of livers obtained from non-heart-beating cadaver donors (NHBD) with the use of core cooling method is presented here. Six livers procured from such cadavers were transplanted into 6 recipients with hepatoma involving right and left lobes but without distant metastases. The first liver subjected to 75 minutes of warm ischemia had insufficient function after transplantation. The recipient died of graft failure 54 days later. The other 5 livers with 32 to 45 minutes of warm ischemia had a good or excellent immediate function. These 5 recipients died of tumor recurrence, acute rejection or septicemia 131 to 261 days after transplantation. The utilization of selected NHBD is suggested by our practice as a possible approach to help alleviate the acute organ shortage in the areas where heart-beating cadaver donors of brain death are not available.

Key words: *Non-heart-beating cadaver donor, Core cooling, Orthotopic liver transplantation*

For the past 20 years, 64 orthotopic liver transplantations (OLT) have been performed in China (Table 1). Although "brain death" has been accepted medically in China since 1975, there is no special law that recognizes it as a criterion for this purpose. It is necessary to wait for cardiac arrest before proceeding with the removal of organs for transplantation. In this report, we present the experience of 6 OLT in the use of livers from non-heart-beating cadavers. This clinical trial has been carried out at the Department of Surgery, Rui Jin University Hospital, Shanghai Second Medical University in Shanghai, China.

Table 1. Orthotopic Liver Transplantation in China

	No. of Cases	Survival		
		1/2 Yr	1 Yr	2 Yr
Hepatoma	50	24	21	5
Cholangio-CA	6	6	—	—
Wilson's Disease	3	1	2	—
α_1-antitrypsin Deficiency	1	—	1	—
Biliary Atresia	3	1	—	2
Budd-Chiari	1	1	—	—
Total	64	33	24	7

MATERIALS AND METHOD

The criteria for the selection of non-heart-beating cadaver donors (NHBD) were as follows: (1) irreversible brain damage (neurological diagnosis), (2) young age (18—25), (3) healthy, (4) the duration of hypotension (systolic B.P. less than 80 mmHg) no more than 30 min and urine output greater than 30 ml/hr prior to cardiac arrest.

At the time of arrival at the Emergency Room, the donors received life-support including artificial ventilation, fluid infusion and inotropic support. Before cardiac arrest, these donors were transferred to the operating room for medical surveillance. The victim's family were consulted with a view to organ donation. When the family's consent was obtained, all life-support excepting artificial ventilation was removed. The organ procurement was started immediately after the pronouncement of the cessation of heart-beat. The portal vein (PV) catheterization was effective 10 to 15 min after cardiac arrest. The use of 5% albumin Sacks solution (4°C) for cooling perfusion can decrease liver core temperature down to 8° to 10°C in 10 min monitored by the thermo-couple-meter (Electrolaboratoiet El-lab Type 3). After removal, the liver was placed in a double-layer plastic bag with icy saline, and preserved in an insulated box containing crushed ice for later use.

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To determine whether the human liver obtained from NHBD would function well, we evaluated the following parameters daily after transplantation for 7 days: volume of bile output, serum bilirubin, SGPT, glucose, alkaline phosphatase, potassium and coagulation system. Liver biopsies were taken during the procurement and transplantation after revascularization. Liver Specimens were kept at autopsy. All were sent for pathological and electron microscopic examination.

All recipients had hepatoma involving both right and left lobes but without clinical evidence of distant metastases (Table 2). The OLT technique and procedure followed those of Starzl et al[8].

Table 2. Recipient Condition

Patient No.	Age & Sex	Disease
OL-1	42 male	Hepatoma
OL-2	22 male	Hepatoma
OL-3	24 male	Hepatoma
OL-4	32 male	Hepatoma
OL-5	27 male	Hepatoma
OL-6	26 male	Hepatoma

Recipient immunosuppressive protocol

Pre-treatment: Cyclophosphamide (CTX) was given (200 mg/day i.v.) for 3 days prior to surgery.

Intra-operative treatment: CTX 100 mg i.v. and 6-methyl-prednisolone (6-MP) 500 mg intravenous infusion were given before and after revascularization during operation.

Posttransplant treatment: Basic immunosuppression consisted of CTX, azathioprine (Aza), steroid and antilymphocyte globuline (ALG). CTX 200 mg/day i.v. was continued for 3 days, then converted to Aza. The dose was 3 to 5 mg/kg/day per os, depending on leukocyte counts. A dose of 6-MP was decreased daily from 500 mg/day to 20 mg/day in 2 weeks. Thereafter, prednisone was given orally starting at 20 mg/day and decreased gradually to a maintenance dose of 5 to 10 mg/day. ALG was administered intravenously (1.0 g/day) 7 to 14 days.

Management of rejection: If there was evidence of acute rejection the 6-MP (500 mg/day) was given over a 3-day period. When signs of remission appeared after the third pulse infusion the dose was reduced by 150 mg daily until 100 mg/day, and then by 20 mg daily down to 20 mg/day, and substituted with prednisone.

Table 3. Summary of Results of 6 Patients Received livers from Non-Heart-Beating Cadaver Donors

Case	Blood Type		Donor Liver			Survival (days)	Main Cause of Death
	D	R	Warm Ischemia Time (min)	Total Ischemia Time	Function		
OL-1	A	A	75	3hr 10min	Poor	54	Ischemic damage of graft
OL-2	O	O	32	2hr 21min	Excellent	139	Acute rejection
OL-3	O	A	36	3hr 31min	Excellent	200	Fulminating infection and septicemia
OL-4	B	B	42	4hr 08min	Excellent	261	Tumor recurrence
OL-5	O	O	38	2hr 43min	Excellent	131	Hepatic failure (hepatitis)
OL-6	B	B	45	5hr 56min	Good	155	Tumor recurrence

RESULTS

Ischemic time of grafts is shown in Table 3. The stage of hypotension in 6 donors before cardiac arrest was between 15 to 30 min. The warm ischemic time (WIT) ranged 32 to 75 min, and total ischemic time (TIT), 2 hr 21 min to 5 hr 56 min (Table 3).

The first liver, after revascularization, appeared to have mild congestion with rather hard and scattered yellowish patches on the surface. The biopsy specimen showed diffuse intra-hepatic hemorrhage and massive necrosis under light microscopic examination, and severe swollen mitochondria, increased lyzosome and chromatin condensation under electron microscopic examination (Figs. 1, 2). The other 5 livers were pinkish in color, and soft. The biopsy specimens showed only a mild depletion of glycogen in hepatocytes with some lymphocytes infiltration in the portal areas, and almost intact organelle structures under electron microscopic examination.

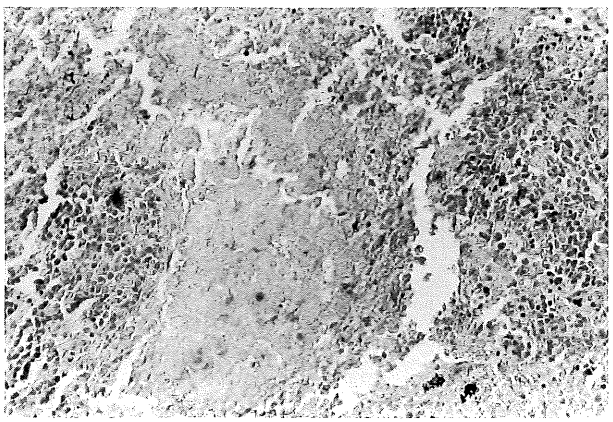

Fig. 1. Specimen from the first liver with 75 min of WIT after revascularization showed a massive coagulation necrosis with recent hemorrhage. Normal liver structure is not seen.

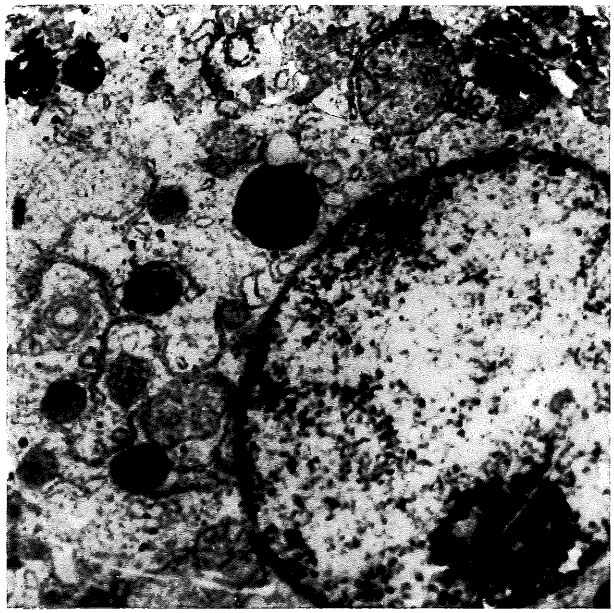

Fig. 2. Liver tissue for electron microscopic examination revealed a swollen mitochondria, increased lyzosome and chromatin condensation along nuclear membrane.

There was no operative death. The hemodynamic and physiologic disturbances usually developed in the anhepatic stage. Severe bleeding and a decrease in venous return to heart resulting from the occlusion of PV and inferior vena cava (IVC) were the main causes of hypotension during the operation. Rapid transfusion of blood was needed to restore blood pressure. Hyperkaliemia, hyperglycaemia, acidosis and shortening of euglobulin lysis time (< 40 min, normal > 120 min), and prolonged prothrombin time (PT) varied in degree from case to case. However, most of these metabolic abnormalities were easily corrected by intensive therapy and returned to normal in 2 to 4 hr after operation except for case 1 which received the liver subjected to 75 min of WIT. Data are summarized in Table 3.

All 6 patients recovered consciousness from anaesthesia 1 to 3 hr after operation without any neurologic or psychologic dysfunction. In the first case who received the liver considered to be irreversibly damaged the graft had no bile excretion after revascularization. The patient had a progressive increase in serum bilirubin (1.5 — 5.0 mg/dl), SGPT (150 — 300 u/dl, normal < 40 u/dl) from the second day posttransplant. Hyperglycaemia (400 — 500 mg/dl), hyperkaliemia (5.3 — 6.0 mEq/liter), acidosis (pH 7.34, pC02 23.6 mmHg, BE —7.2) and a prolonged PT (28 — 41 sec, normal = 12 sec) have not since been corrected during whole postoperative period. One month later, the graft function deteriorated progressively with the appearance of deep jaundice and massive ascites. The patient died of hepatic failure and GI bleeding on the 54th posttransplant day. Necropsy showed that the liver to be a dark purple color, with hard consistency, irregular necrotic patches and inspissated sludge throughout the biliary tract. The other 5 patients who were transplanted with livers having 32 to 45 min of WIT were unremarkable. All the 5 grafts had good or excellent functions with slight changes of serum K, bilirubin and SGPT, and normal histological structures after transplantation. They died 131 to 261 days after transplantation due to irreversible acute rejection, septicemia or hepatoma

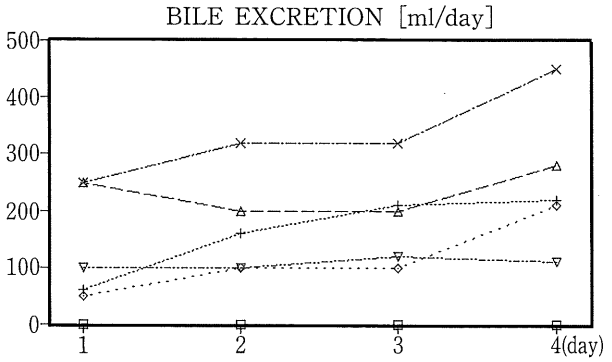

Fig. 3. Bile excretion in the first 4 days after transplantation.

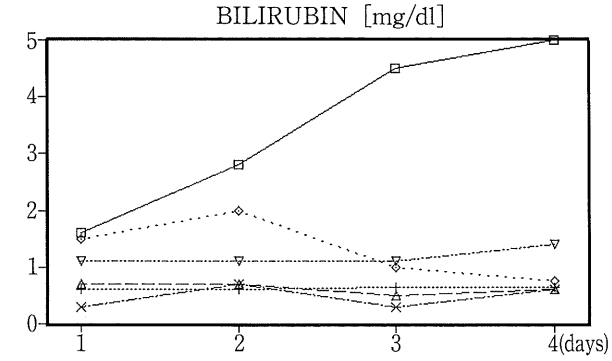

Fig. 4. Serum bilirubin levels in the first 4 days after transplantation.

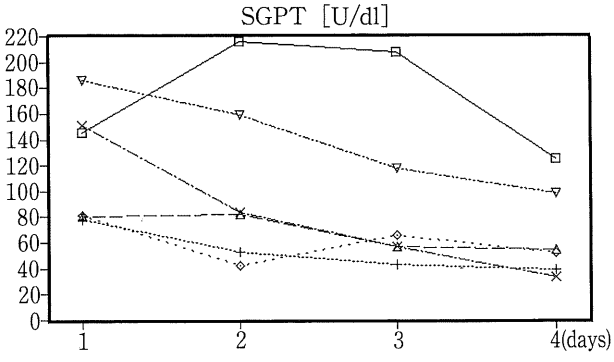

Fig. 5. SGPT levels in the first 4 days after transplantation.

recurrence (Table 3). Figures 3, 4, 5, show the functions of these 6 livers within 4 days posttransplant.

DISCUSSION

Because of the shortage of organs from brain death with heart-beating cadavers (HBC), it is necessary to use every available organ even in the United States. The Nashville Regional Organ Procurement Agency has procured 166 kidneys from 83 NHBD by the use of triple lumen, double balloon Garcia-Lefrak catheter (GLC) inserted into aorta through femoral artery for in situ renal cooling. Eighty-two kidneys with WIT less than 15 min were transplanted. The immediate function was 30.6% which was lower than that (53.6%) in HBC kidneys. But 1- and 2-year graft survival showed no difference[4]. Fujita et al[2] in Japan reported that 122 kidneys were harvested from cardiac-arrest donors for transplantation. In situ cooling of kidneys with GLC technique was started at 2 to 85 min (mean ± SD = 17.3 ± 20.2 min) after cardiac arrest. Of 122 kidneys, 108 kidneys were transplanted into 108 chronic hemodialysis patients. The recovery of renal function was 89.6% during an average of 0 to 103 days (mean ± SD = 14.4 ± 17.5 days) in the CyA group and 78% during an average of 0 to 28 days (mean ± SD = 10.2 ± 6.8 days) in the non-CyA group. These studies indicated that it is possible to use kidneys taken from NHBD for transplantation. The liver is much more sensitive to hypoxia than the kidney. While the heart beat existed in accident victim, the liver almost certainly suffered ischemic damage due to prolonged hypotension and deoxygenated acidic blood perfusion. This renders it impossible to use many of these potential donors. For how long the human liver can tolerate warm ischemia is still an open question. Twenty min is generally accepted to be the "safe period" for human liver blood flow occlusion[5]. Kahn et al[5] reported a clinical case which recovered uneventfully from 90 min of WIT to the liver due to an accident ligation of portal triad in gastric surgery. Hoshino et al[3] have compared two different methods: total body hypothermia through cardiopulmonary bypass (CPB) and flush technique (FT). In the latter method the liver was flushed and cooled with cold solution via the aorta and the splenic vein. According to their data taken from pig studies, by the use of CPB, the livers taken from NHBD with 5 and 10 min cardiac arrest or 30 min hypotension and 5 min cardiac arrest had perfect immediate function after transplantation sufficient to support the recipients for 4 days. However, livers harvested from NHBD by FT were unsuccessful. It has been previously confirmed by our initial clinical trial in 6 OLT that the human liver from selected NHBD can be expected to retain its immediate life-sustaining functions after transplantation if the period of hypotension is limited within 30 min and WIT, within 32 — 45 min. Rapid core cooling via PV is effective in keeping a quick decrease in liver core temperature down to 8° to 10°C in 10 min. We recognized that the selection of donors and rapid core cooling method are two important processes and procedures for the use of livers from NHBD. It should be emphasized also that a second period of WIT in the course of recipient operation could be harmful for the liver. We found that the core temperature of the first liver rose rapidly from 4°C to 32.5°C in 21 min after removal of the liver from storage and placement into recipient abdominal cavity. The first liver succumbed to 2 periods of warm ischemic damage, 35 min in the harvesting and 40 min in the transplantation. To minimize this, we recommend that a continuous core cooling and surface rinsing with cold saline should be implemented until the reflow of PV. Recently some reports[1,6,7] have suggested that the administration of free radical scavenger compounds can inhibit oxygen free radicals in rat liver and limit the process of cell damage, such as coenzyme Q10 (CoQ10) and superoxide dismutase (SOD). The pretreatment of CoQ10 (10 mg/kg i.p. one day before inducing ischemia) can improve the survival rate in rats whose livers have been subjected to 90 min of WIT from 0% in non-treated rats to 58%[6,7]. The use of drugs with antioxidant, membrane-stabilizing properties might be expected to assist in the prevention of human liver from warm ischemic damage in NHBD.

We conclude that the use of liver from selected non-heart-beating cadaver donors for clinical transplantation is feasible. The guiding principles for the utilization of such cadaver donors are as follows: (1) young healthy donors, (2) hypotension episode of no more than 30 min and sufficient urine output prior to cardiac arrest and (3) controlled WIT within 60 min.

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