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## MODIFIED SIMPLE COLD STORAGE OF RAT LIVERS WITH UW SOLUTION<sup>1</sup>

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Rat livers were preserved with the conventional use of UW solution for 30, 42, and 48 hr and compared with livers in which the vascular bed was expanded with an additional 10 to 60 ml UW/100 g liver. The extra UW, expressed as % liver weight, was entrapped during final portal infusion by tying off the supra- and infrahepatic inferior vena cava. A beneficial influence of the vascular expansion was most pronounced in the 40% group, with 10/10, 5/10, and 3/10 long-term survivors following transplantation after 30, 42, and 48 hr preservation versus 3/10 and 0/10 after 30 and 42 hr in the 0% controls. In separate experiments, surrogate indices of preservation quality following reperfusion explained this effect. The 40%—and, to a lesser extent, 20%—livers had higher and more uniformly distributed portal blood flow, better tissue oxygenation, smaller increases in postperfusion liver enzymes, higher adenine nucleotides and energy charge, and less histopathologic evidence of hemorrhage and congestion. Pressure changes in the vena cava fluid sump in additional experiments indicated that retrograde

infusion of the trapped UW solution occurred in all of the 10–60% groups during the first 6 hr with stable pressures of 1.5 to 3 cm H<sub>2</sub>O thereafter. Collectively, these data suggest that the much discussed selective vulnerability of the microvasculature of stored allografts is due in part (or principally) to its selective lack of long-term exposure to the UW solution, which drains out of the open vessels but not from the parenchyma. The potential clinical exploitation of this concept is discussed.

Recent literature has emphasized microvascular injury as the principal limitation of static cold liver preservation (1–3). With these methods, the preservation solution does not thoroughly fill the microvasculature and remain there. With the hypothesis that microvasculature collapse during the preservation deprives the vessels of benefit from the preservation fluid and increases the resistance for the reperfusion blood flow, we tested a modification of the standard technique. In our experiment, different amounts of UW solution were infused into preserved rat livers, followed by occlusion of all vessels in order to trap the fluid within the vasculature at all levels. The results after orthotopic transplantation were com-

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pared with those using the conventional static preservation technique for various durations.

### MATERIALS AND METHODS

**Animals.** Male Lewis rats, weighing 225 to 300 g, were used for donors and recipients, housed in individual cages, and fed ad libitum until the night before the experiment.

**Operative procedures.** Orthotopic rat liver transplantation was performed by the method of Kamada et al., without reconstruction of the hepatic artery (4). Donors were anesthetized by intraperitoneal injection of 50 mg/kg sodium pentobarbital. After ligation of the phrenic veins, the donor liver was flushed with 5 ml of cold UW solution through a catheter inserted in the abdominal aorta. The organ was then removed, with precautions not to injure the hepatic capsule. After hepatectomy, the liver was flushed again with 2.5 ml UW solution via the portal vein. It was weighed and placed into a container filled with UW solution and kept at 4°C in a refrigerator until transplantation. Immediately before transplantation, the graft was flushed with 5 ml of cold lactated Ringer's solution. The vena caval effluent from the terminal flush was collected and stored at -20°C for enzyme analysis (SGOT, SGPT, LDH). Before closure of the abdominal wall, 5 ml of normal saline and 50 mg/kg of cefamandole nafate were given to recipient animals.

**Experimental groups.** After the removed graft was flushed with UW solution, both the suprahepatic and the infrahepatic vena cava were ligated with 6-0 silk ties. Then an additional amount of UW solution was infused to the graft via the portal vein, which also was ligated after the infusion. The amount of infused additional UW solution was calculated by the formula: liver weight (grams)  $\times$  0% to 60% (ml/g). The livers were randomly sorted into 7 groups according to the amount of additional UW solution infused: 0% (control), 10%, 20%, 30%, 40%, 50%, and 60%. For example, a liver weighing 10 g in the 40% group would be given 4 ml entrapped UW solution—or, in terms extrapolated to large animals or humans, 40 ml/100 g liver tissue.

**Survival experiments:** A total of 10 livers from each group were preserved for 30, 42, or 48 hr and orthotopically transplanted. The cause of all subsequent deaths was determined and animals that survived were sacrificed for pathologic study after 3 postoperative weeks.

**Studies during preservation:** In separate experiments, the changes of graft weight and hepatic venous pressure were determined during preservation of 5 livers from each of the 7 groups during 48-hr preservation. After tying the vena caval but before infusing additional UW solution, a 20 cm polyethylene tube (PE200, O.D. 1.9 mm) was inserted into the suprahepatic vena cava, and kept vertical to the horizontal plane so that the hepatic venous pressure could be measured directly by the height of the fluid column, and expressed as cm H<sub>2</sub>O. These venous pressures (P) as well as graft weight were measured at 10, 20, 30, and 60 min, and every 6 hours thereafter. After 48 hr, the ties in the vena cava and portal vein were released, allowing the trapped solution to flow out.

Three sets of graft weights were obtained: (1) the initial one (W<sub>i</sub>) after the back table flush; this weight was used to calculate the amount of UW in the entrapment infusion; (2) the weight during the fluid entrapment (W), which invariably declined, reflecting the water leak through the capsule that is characteristic with UW; and (3) the final net weight (W<sub>n</sub>) after the vessel ties were released, allowing the trapped UW to flow out.

**Graft reperfusion studies:** In a further separate experiment, livers were preserved for 30 hr and transplanted orthotopically. Then 60 min later, hepatic blood flow was measured and the animals were sacrificed for blood and tissue samples (see below).

**Postperfusion physiologic and chemical studies.** The detailed postperfusion studies were performed on 5 livers each from the 0%, 20%, 40%, and 60% experimental series in which the experiments were terminated 60 min after orthotopic transplantation of 30-hr-preserved livers.

**Portal and tissue blood flow:** A control value in the recipient was measured before hepatectomy but after hepatic artery ligation. At 5, 15, 30, and 60 min after revascularization of the graft in the recipient, the portal venous blood flow was measured with a Transonic HT 101D flowmeter (Transonic System Inc., Ithaca, NY) and expressed as ml/min/g of initial graft weight.

The index of tissue oxygenation (IS<sub>O2</sub>) and the index of regional blood flow (IH<sub>b</sub>) were also studied at all of these same times by the method of Sato et al. (5, 6), using a tissue spectrum analyzer TS-200 (Sumitomo Electric Inc., Osaka, Japan). In addition, these tissue measurements were performed on the intact (arterialized) recipient liver before hepatectomy (basal value). Each measurement included points on the right, median, and left lobes; the 3 values were averaged.

**Oxygen consumption:** After 60 min reperfusion, blood samples drawn from the portal vein and the hepatic vein were analyzed for partial pressure of oxygen (PO<sub>2</sub>), hemoglobin (Hb), and percentage saturation of the hemoglobin (Sat). These were measured with the Radiometric of Copenhagen acid-base laboratory ABL2 (Radiometer, A/S Emdrupvej 72, DH-2400 Copenhagen, NV, Denmark). The oxygen consumption of the graft was calculated by the Fick equation =  $Q \times (C1 - C2)$  in which Q is portal blood flow (ml/min/g), C1 is oxygen content of the portal venous blood, and C2 is the oxygen content of hepatic venous blood. The oxygen content =  $(1.39 \times Hb \times Sat/100) + 0.003 \times PO_2$  (7).

**Liver enzymes:** The serum level of GOT, GPT, and LDH were measured in inferior vena caval samples after 60 min of reperfusion with the Technicon RA-500 autoanalyzer (Technicon, Tarrytown, NY). The same instrument was used to measure these enzymes in the effluents that were collected at the end of preservation of survival experiment livers.

**Adenine nucleotides:** At 60 min after reperfusion, liver biopsies were taken with forceps precooled in a liquid nitrogen, and stored in liquid nitrogen (-70°C) until analysis. Adenosine nucleotides (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) were measured with a high-performance liquid chromatography (Waters Chromatography Division, Millipore, Milford, MA) on an anion exchanger column, DEAE-2SW (4.6 $\times$ 250), equilibrated with 0.15 M phosphate buffer, pH 5.65. Energy charge (EC) was calculated as  $EC = ([ATP] + 0.5 [ADP]) / ([ATP] + [ADP] + [AMP])$  (8).

**Histopathologic study:** At the end of the 60-min reperfusion, tissue samples were fixed in buffered formalin and stained with hematoxylin-eosin. Histopathologic changes were analyzed without knowing the group from which the samples came.

**Statistics.** Data were expressed as the mean and standard error of the mean. Animal survivals were compared using a Fisher's exact test. Group comparison of the other studies were performed by a Student's *t* test. A probability value less than 0.05 was considered significant.

### RESULTS

**Survival studies.** With 30-hr-preserved livers, only 3 of the 10 animals in the 0% (control) group lived for 3 weeks, while all of the 30% and 40% group animals lived this long (Table 1). When preservation time was prolonged for 42 hr, the only 3-week survivors were in the 30% and 40% group. Even after 48-hr preservation, 3 animals in the 40% group survived for 3 weeks. The obvious cause of mortality in most of the animals was liver failure 1 to 2 days after transplantation.

To avoid manipulating these animals, bleeding for postoperative biochemical studies were not done. As a compromise, GOT, GPT, and LDH were measured in the graft effluent at the end of preservation. Compared with the 0% (control) group, these were lowest in the 40% group ( $P < .05$ ) and second lowest in the 20% group (Fig. 1). The 60% group had high enzymes in the effluent—and although these were not sta-

TABLE 1. Survival after orthotopic rat liver transplantation

Preservation time (hr)	Groups (10 recipient rats in each group)						
	0%	10%	20%	30%	40%	50%	60%
30	3	3	8	10**	10**	6	2
42	0	0	0	2	5*	0	0
48				1	3		

\*  $P < 0.05$  vs. 0% group.

\*\*  $P < 0.01$  vs. 0% group.

tistically significant compared with the 0% controls, they suggested that leakage of enzymes had occurred during preservation.

**Studies During 48-hr preservation.** Weight: All liver groups lost weight between the time of their initial (Wi) and final (Wn) weighing, with a consequent Wn/Wi ratio less than 1.0 (Table 2). This weight loss was less in all fluid entrapment groups than in the 0% controls, and significantly so ( $P < 0.05$ ) in livers in which the sequestered UW solution was 40% of the liver volume; these livers lost only 5.5% of their original weight compared with 14.9% in the 0% nonsequestration controls.

The dynamics between these beginning and end points could be inferred from the difference between the liver weight with its encapsulated UW solution (W) and the fixed initial weight (Wi) at successive times during the 48-hr preservation

TABLE 2. Wn/Wi ratio using different volumes of entrapped UW solution during 48-hr preservation

Volume UW (% Wi)*	Wn/Wi
0% (control)	0.820 ± 0.014
10%	0.855 ± 0.010
20%	0.888 ± 0.006
30%	0.912 ± 0.016
40%	0.924 ± 0.007*
50%	0.920 ± 0.019
60%	0.881 ± 0.035

\* Wi=initial liver weight.

Wn=final liver weight after draining entrapped UW solution.

\*  $P < 0.05$  versus 0% (control) group.

(W/Wi ratio). In the 0% (control livers), a time-related dehydration was evident (Fig. 2). The extra weight added by increasing volumes of entrapped UW solution began to diminish with time after 20 min in all fluid entrapment groups. In the 50% and 60% groups, lymphlike droplets were grossly apparent on the liver capsule, suggesting transhepatic water passage.

**Vena caval pressure:** The pressure findings were congruent with the liver weight measures (Fig. 3). Pressures were elevated in proportion to the entrapped volume of UW solution, but these fell to a common level in the 1–3-cm H<sub>2</sub>O range between 0 time and 6 hr.

**Reperfusion studies for 60 min after 30-hr preservation.** Portal and tissue blood flow: Although graft portal flow under all conditions was inferior to that measured to the native recipient liver before its excision, the 40% livers had nearly 3

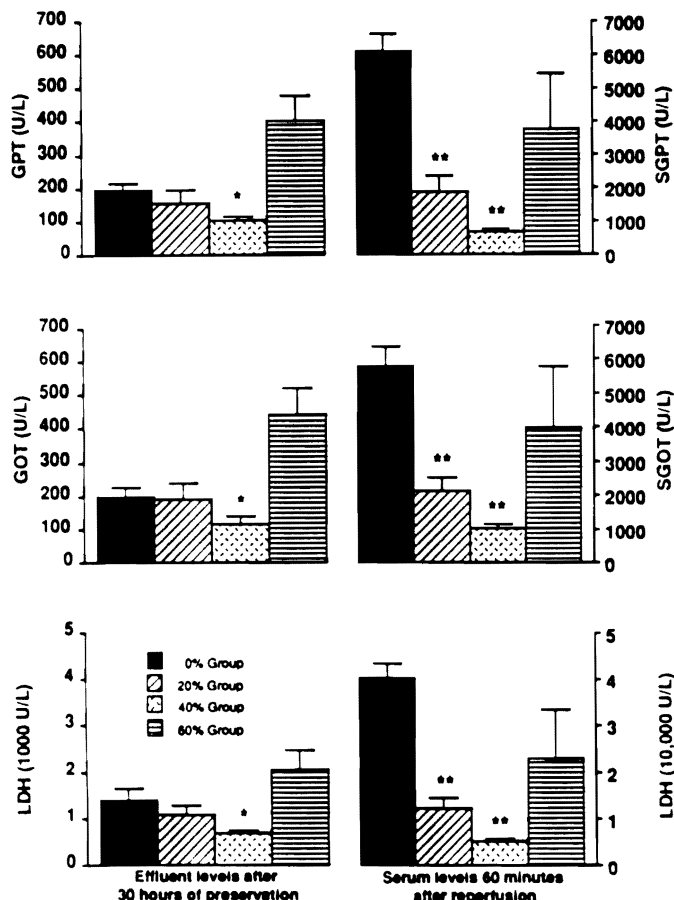


FIGURE 1. GPT, GOT, and LDH in perfusate after 30-hr preservation (left panel), and in serum drawn during the 60 min of reperfusion of 30-hr-preserved livers (right panel). (\*)  $P < 0.05$  vs. 0% group, (\*\*)  $P < 0.01$  vs. 0% group.

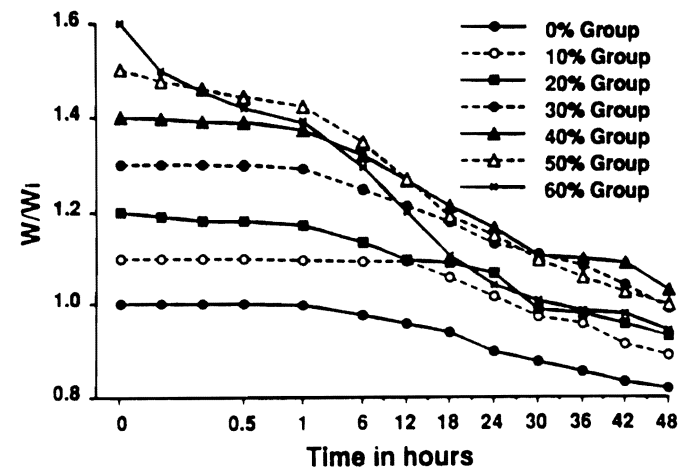


FIGURE 2. The changing weight over 48-hr preservation of the liver and its trapped UW solution (W)/versus the initial prepreservation weight (Wi), expressed as W/Wi ratio. The variable amounts of sequestered UW solution in ml/100 g liver tissue are expressed as 0–60%; 0% is control (no UW added).

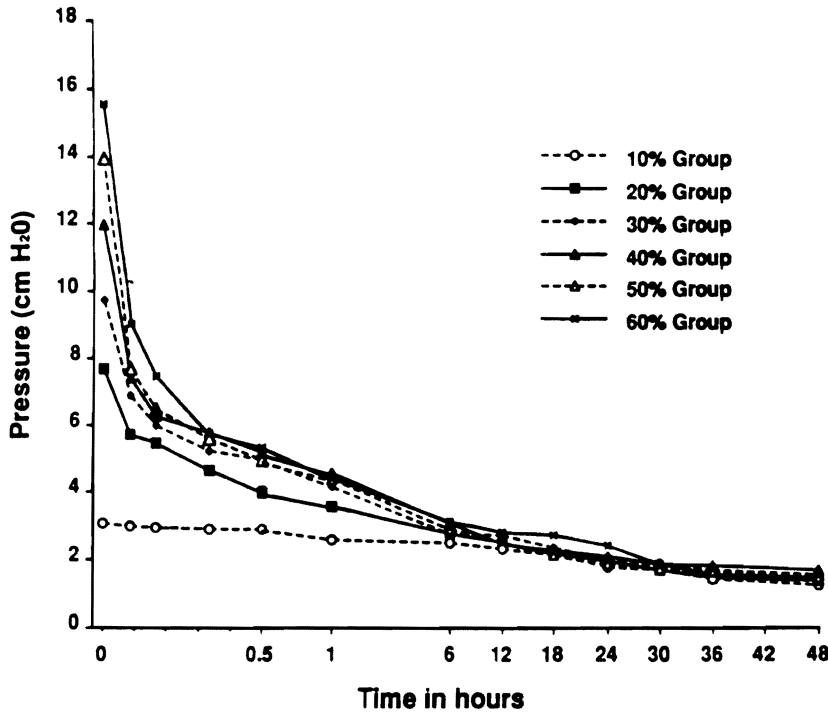


FIGURE 3. Changes over 48-hr preservation of the vena caval (hepatic venous) pressure after instilling and entrapping variable quantities of UW solution as in Figure 1.

times the flow as the 0% organs 5 min after reperfusion ( $P < 0.01$ ), and a 6 times advantage at 60 min (Fig. 4). The less-satisfactory 20% livers, but not the 60% livers, also were significantly better than controls at 5 min ( $P < 0.05$ ).

Tissue oxygenation ( $ISO_2$ ) was significantly higher in the 40% group ( $P < 0.01$ ) than in the 0% group during all 60 min of reperfusion (Fig. 5) as was the index of regional flow (IHb) ( $P < 0.05$ ) during the first 30 min of reperfusion (Fig. 6). All groups were better than the controls.

Oxygen consumption: Oxygen consumption of the 30-hr-preserved livers was markedly higher in the 40% group than in the 0% group ( $P < 0.01$ ). The values (in ml  $O_2$ /min/100 g liver) were  $0.312 \pm 0.0435$ ,  $1.112 \pm 0.423$ ,  $1.918 \pm 0.601$  ( $P < 0.05$  vs. 0% group), and  $0.739 \pm 0.294$  in the 0%, 20%, 40%, and 60% groups, respectively.

Liver enzymes: After the 60-min reperfusion, the serum GOT, GPT, and LDH levels were significantly lower in the 40% group than in the 0% group ( $P < 0.01$ , Fig. 1).

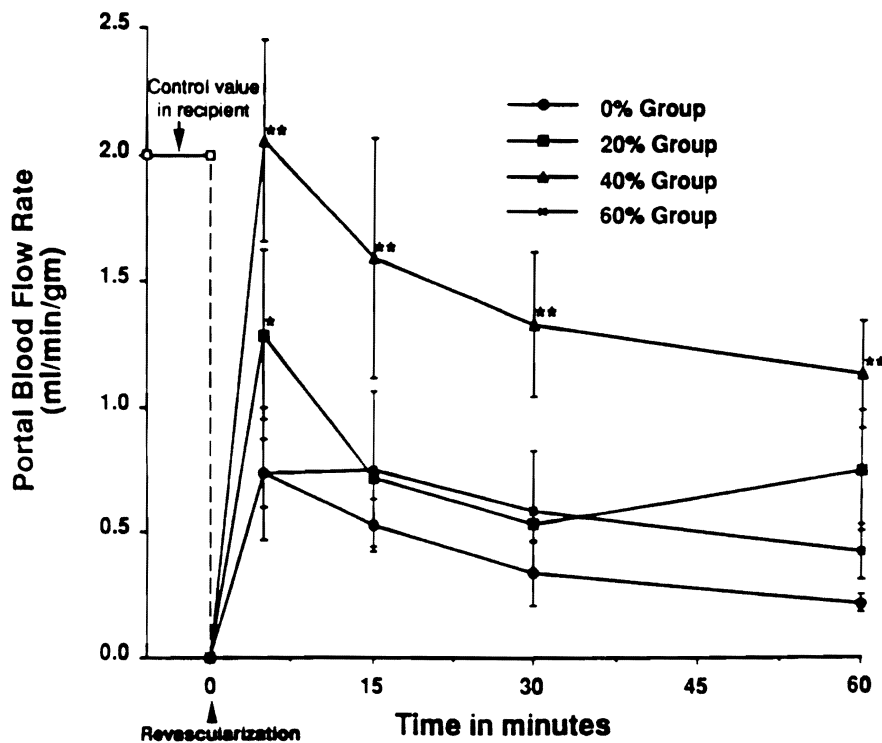


FIGURE 4. Portal blood flow rate during the first 60 min of reperfusion of the 30-hr-preserved livers. (\*)  $P < 0.05$  vs 0% group, (\*\*)  $P < 0.01$  vs. 0% group.

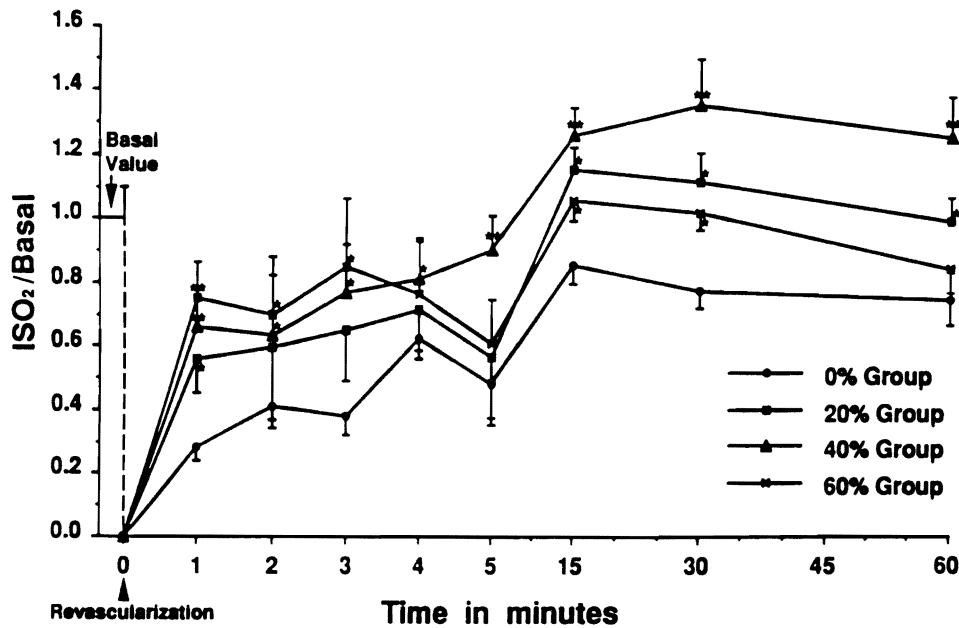


FIGURE 5. ISO<sub>2</sub> (index of tissue oxygenation) during 60-min reperfusion of 30-hr-preserved livers. (\*)  $P < 0.05$  vs. 0% group, (\*\*)  $P < 0.01$  vs. 0% group.

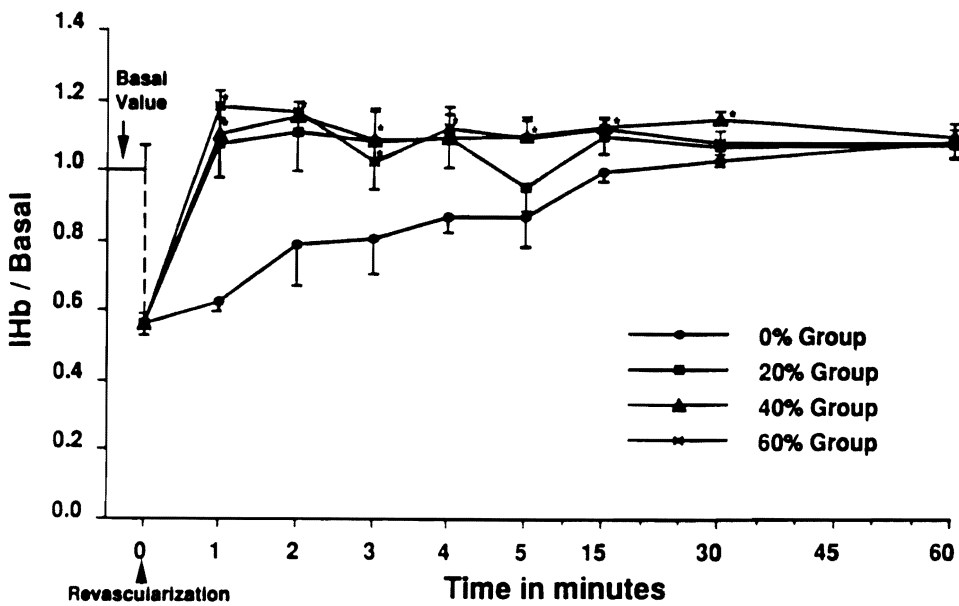


FIGURE 6. IHb (index of regional blood flow) during 60-min reperfusion of 30-hr-preserved livers. (\*)  $P < 0.05$  vs. 0% group.

Adenine nucleotides: ATP, total adenine nucleotides, and energy charge were significantly higher in the 40% group livers than in the 0% group livers after the 60 min of reperfusion (Fig. 7).

Histopathology: Damage of sinusoidal cells and hepatocytes were seen in the 30-hr-preserved livers. Reperfusion for 60 min induced further damage to the liver, but no significant difference was found with light microscopy among these experimental groups. The 40% group livers appeared to have less congestion and hemorrhage than those of the 0% group livers.

#### DISCUSSION

Whether the eventual objective is ex vivo perfusion or preservation by simple refrigeration, the first step in the procurement of all whole organs is core cooling by the intravascular infusion of chilled solutions. This cardinal principle was first defined with experimental liver transplantation (9), and then

systematically applied to the human kidney (10), and eventually to all other organs (11). With this generic technique, the infusion fluid that has reached the interstitial space remains there throughout the period of static preservation. However, the macro- and microvasculature can freely drain their fluid, creating the possibility that the preservation environment of their lining endothelial cells is inferior to that of the parenchymal cells.

In the study reported here, we asked if UW solution, the current best infusate for initial cooling and for static refrigeration of the liver (12, 13)—and probably other organs (14–16)—could be made more effective with improved conditions of fluid delivery and retention. The modifications were evaluated by the ultimate test of survival after actual transplantation, and with surrogate chemical and metabolic indices.

In our experiments the vascular bed of the liver was expanded with an entrapped amount of transportally delivered UW solution, equivalent to 10 to 60 ml/100 g hepatic tissue.

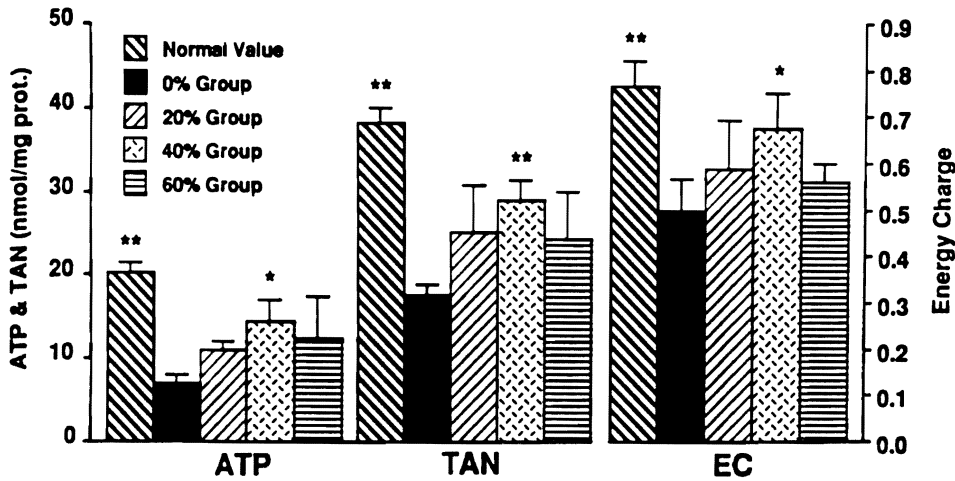


FIGURE 7. ATP, TAN, and EC after the 60-min reperfusion of 30-hr-preserved livers. (\*)  $P < 0.05$  vs. 0% group, (\*\*)  $P < 0.01$  vs. 0% group.

The normal blood volume of the liver is 25–30 ml/100 g (17), which can be more than doubled if there is a high outflow or elevated central venous pressure (18). The tied-off inferior vena cava in our model served as a dampening volume reservoir from which pressure was relieved by retrograde perfusion.

This vascular expansion appeared to be a beneficial adjunct to the UW solution by all outcome indices, the optimal volume expansion being 40 ml/100 g liver tissue (40% groups). The most important pragmatic observation was that survival after transplantation was possible following preservation for durations that made this unlikely or precluded it altogether using UW alone. The surrogate measures of preservation quality explained why. Although the livers had less enzyme leak during the preservation, the key factor appeared to be greatly improved reperfusion immediately after revascularization and subsequently. There was higher total portal blood flow that was uniformly distributed peripherally, better tissue oxygenation, more oxygen consumption, and smaller increases in the postperfusion hepatic enzymes. At the end of 60 min, the liver adenine nucleotides and energy charge were higher than in controls, and histopathologically the livers had less congestion and hemorrhage.

Smaller benefits also were evident when the liver was suboptimally expanded with 20 ml/100 g but not with volumes less than this. Overfilling of the liver to 60 ml/100 g was not overtly harmful, although there was a trend toward greater release of the hepatic enzymes used to quantitate tissue damage. Concerns about the injurious effects of impeded venous outflow have been pervasive in the preservation literature, stemming in part from the early recognition of the lethal complication of "outflow block" in the canine liver (9) and the later perception that other organs such as the pancreas were exquisitely intolerant to transient elevations of venous pressure (19). Thus, the possibility that extrapolation of the rat data to clinical application could be a miscalculation mandates confirmatory experimentation on dogs or other larger animals.

Nevertheless, the internal harmony of our observations makes some kind of clinical application likely. It is now well accepted that endothelial damage to the vessels within the liver and other organs, rather than irreversible injury to the parenchymal cells, is the limiting preservation factor (1–3). The consequent hypoperfusion after revascularization per-

petuates damage to the distal tissues instead of allowing recovery (3). After instillation of 40 ml/100 g liver tissue, an autoregulatory adjustment occurred in our experiments conducive to uniform exposure of all cells to the infusate. No matter how great the volume of fluid instilled into the closed system, the pressure measurements in the vena cava indicated rapid equilibration throughout the specimen, apparently by retrograde perfusion. This was consistent with the seemingly paradoxical (at the time) report by Lui et al. (20) that better preservation results could be obtained with retrograde infusion of the rat liver through the tied-off vena cava than using the conventional portal route.

Aside from the uniform exposure of the entire graft to the preservation solution, our technique could facilitate reperfusion as a direct expression of a physics principle. Burton has described the difficulty of re-expanding flexible conduits once they have collapsed below a point defined as the "critical closing pressure" (21). Variable avoidance of this would be expected with our technique depending on the fluid volume used. The prompt "red" suffusion of the optimally preserved transplanted livers in our studies compared with the more patchy appearance in the controls was consistent with such a benefit. Although these comparative observations were subjective, they were confirmed by objective measurements showing a uniform reperfusion flow in all regions of the transplanted livers.

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## CHANGES IN HEMODYNAMIC AND METABOLIC PARAMETERS FOLLOWING INDUCED BRAIN DEATH IN THE PIG<sup>1</sup>

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Changes in hemodynamic and metabolic parameters (systemic oxygen delivery,  $[\text{DO}_2]$ , oxygen consumption  $[\text{VO}_2]$ , arterial lactate content) in brain-dead and control pigs in the absence of any inotropic or fluid support were studied. Brain death was induced by the inflation of a Foley catheter balloon placed into the subdural space of the animals. Serial atrial natriuretic peptide (ANP) determinations were performed to evaluate concomitant changes occurring in the endocrine function of the heart. Experiments were completed by a volume expansion protocol to provide a dynamic evaluation of these parameters. A significant

increase in heart rate (from  $113 \pm 5$  to  $176 \pm 11$  beats/min), pulmonary capillary wedge pressure (from  $7 \pm 1$  to  $12 \pm 3$  mmHg),  $dP/dt$  (from  $2040 \pm 340$  to  $4200 \pm 660$  mmHg/sec<sup>-1</sup>), cardiac output (from  $2.4 \pm 0.2$  to  $3.3 \pm 0.4$  L/min), mean arterial pressure (from  $66 \pm 8$  to  $93 \pm 14$  mmHg), and systemic oxygen delivery (from  $360 \pm 30$  to  $530 \pm 90$  ml/min<sup>-1</sup>), was observed following brain death induction. These parameters returned below basal values within 60 min. On the contrary, serum lactate and  $\text{VO}_2$  remained unchanged. Following volume expansion, brain-dead pigs exhibited impaired hemodynamic response, with a significant decrease in  $dP/dt$ , MAP, and  $\text{DO}_2$ . These changes were accompanied by a significant decrease in  $\text{VO}_2$ , and a significant increase in lactate plasma levels. At the same time, a similar increase in ANP release was observed in both groups in response to volume expansion, suggesting that despite impaired myocardial contractility, endocrine function of the heart was preserved following brain death. We conclude that brain death leads to early impaired left ventricular contractility, which could be responsible for the changes observed in aerobic to

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