Disturbance of Microcirculation Associated With Prolonged Preservation of Dog Livers Under University of Wisconsin Solution


RECENTLY we reported that, in human liver transplantation, a preservation period of greater than 20 hours caused the rate of graft failure to increase nonlinearly. Even with University of Wisconsin (UW) solution, there is a finite limit to the permissible time of cold storage of livers. In this study, we investigated whether microcirculatory disturbance during and after preservation is correlated to cold ischemia and graft outcome.

MATERIALS AND METHODS
Orthotopic liver transplantation in dogs was performed by the method described previously, but with minor modification. Inbred female beagle dogs weighing 9 to 13 kg were used for recipients, and 7- to 10-kg dogs were used for donors. The donor liver was perfused in situ with 2 L of UW solution before orthotopic transplantation, with the preservation period of 0 hours: immediate transplantation (group 1, n = 9), 24 hours (group 2, n = 7), or 48 hours (group 3, n = 7). Two-week animal survival was determined.

In separate acute experiments, hepatic blood flow, microcirculation, and histology were studied at the end of preservation and shortly after graft reperfusion for preservation periods of 0 hours: immediate transplantation (group 1, n = 9), 24 hours (group 2, n = 9), and 48 hours (group 3, n = 9). The measurement of hepatic arterial and portal vein flow was done with an Ultrasonic Blood Flowmeter (Model T-201, Transonic Systems Inc, Ithaca, NY). Measurements were performed at 1 and 2 hours after graft revascularization and results were expressed as ml/min/g of wet weight. The microcirculation was studied anatomically with the Microfil technique. After the heparatectomy, 20 mL of the red Microfil silicon rubber compound (Flow Tek, Inc, Boulder, Colo) was slowly infused through the hepatic artery. White Microfil (100 mL) was manually infused through the portal cannula, followed by 30 mL yellow Microfil compound. The liver was stored in 25% alcohol for 1 day, and then processed every other day with 50%, 75%, 95%, and 100% alcohol. A 1-mm width of the liver was sliced and cleared with methylsilicate for an additional 24 to 48 hours. The slice was examined under a stereoscopic dissecting microscope. A piece of the left lobe was excised for histologic study. Tissues were fixed with 10% formalin and stained with hematoxylin-eosin. Student t test and analysis of variance were used for the comparison of groups, and a P value less than .05 was considered significant.

RESULTS
In groups 1 and 2, 6 out of 7 dogs survived for 14 days (86%). One dog in group 1 died 7 days posttransplantation of intussusception and the dog in group 2 died 1 day posttransplant due to pulmonary edema. In group 3, all dogs died within 2 days, with pulmonary edema being the main cause of death (bloody ascites was seen in 2 dogs). Groups 1 and 2 showed significantly better survival than group 3.

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Groups 2 and 3 had high uptake into the periportal area in the medium and small portal veins compared with group 1. The hepatic artery and bile plexus were well visualized in the portal triad of each group, without statistical differences. Histologically, no morphologic difference could be detected between the groups prior to revascularization. After revascularization, no morphologic change was seen in group 1 except for slight swelling of sinusoid lining cells and minimal vacuola in hepatocytes. However, groups 2 and 3 showed mild to moderate damage of the sinusoid lining cells after revascularization. Group 2 also showed pyknotic nuclei and vacuola in hepatocytes in half of the cases, although necrosis of hepatocytes was rare. In group 3, vacuola in hepatocytes were detected in all cases, and necrosis of hepatocytes in central areas was prominent compared with group 2.

DISCUSSION
There was a marked reduction of animal survival after transplantation of liver grafts preserved for a prolonged period. However, no significant changes, except for some patchy dilatation of sinusoids, were found in groups 2 and 3 by Microfil analysis at the end of the preservation period. After reperfusion, a steep decline of hepatic arterial flow and structural disturbance of the microcirculation were observed. The severity of these changes was correlated with preservation time. These results suggests that, as with kidney preservation, protection from microcirculatory disturbance appears to be an important factor for improved liver preservation.

REFERENCES