

Glucose Metabolism during Liver Transplantation in Dogs

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Arterial and hepatic venous blood levels of glucose were studied in 12 dogs during orthotopic liver transplantation performed under ketamine anesthesia without exogenous glucose administration. During the early part of surgery, arterial blood glucose levels were stable: 161 ± 12 mg/dl (mean \pm SEM) after laparotomy and 183 ± 16 mg/dl 5 min before the anhepatic stage. During the anhepatic stage, arterial blood glucose levels decreased progressively to 135 ± 9 and 88 ± 8 mg/dl, 5 min in the anhepatic stage and 5 min before reperfusion of the graft liver, respectively ($P < 0.05$). Reperfusion of the graft liver resulted in an increase in arterial glucose levels to 206 ± 17 and 240 ± 24 mg/dl, 5 and 30 min after reperfusion, respectively ($P < 0.05$).

Hepatic venous blood glucose levels increased after reperfusion (405 ± 37 and 346 ± 41 mg/dl, 5 and 30 min after reperfusion, respectively) and were significantly higher than in arterial blood ($P < 0.05$). Arterial plasma insulin, measured in five animals, did not change significantly during the procedure, whereas plasma glucagon levels, stable during the preanhepatic and anhepatic stages, increased steadily after reperfusion of the graft liver, from 66.1 ± 14.2 to 108.4 ± 38.1 pg/ml ($P < 0.05$). This study shows that in dogs with ketamine anesthesia mild hypoglycemia occurs during the anhepatic stage of liver transplantation without exogenous glucose administration followed by hyperglycemia on reperfusion of the graft liver, possibly secondary to the release of glucose from the donor liver.

Key Words: ANESTHESIA—liver transplantation. LIVER—transplantation. METABOLISM—glucose.

Significant improvements have been made recently in the surgical and anesthetic management of patients undergoing liver transplantation (1,2). However, understanding of glucose metabolism during liver transplantation is still incomplete. Aldrete et al. saw hypoglycemia frequently, especially during the anhepatic stage of the procedure, and advised that large amounts of exogenous glucose be administered during orthotopic liver transplantation in humans (3). They ascribed the low levels of glucose to the absence of the liver, the main producer of blood glucose. Others have reported that hypoglycemia did not occur when small

amounts of exogenous glucose were administered (4,5). Tullock et al. reported that without administration of exogenous glucose other than that in transfused blood, blood glucose levels remained within an acceptable range during the preanhepatic and anhepatic stages, but that hyperglycemia of more than 200 mg/dl occurred after reperfusion of the graft liver (4).

These differences in clinical experience remain unexplained; glucose metabolism may have been different among individual recipients, and intraoperative management also may have been different. To investigate intraoperative glucose metabolism, we measured blood levels of glucose, insulin, and glucagon in healthy dogs undergoing liver transplantation without exogenous glucose infusion.

Methods

Orthotopic liver transplantation was performed in 12 adult beagle dogs, weighing between 11.0 and 14.0 kg (mean 11.9 kg). The animals fasted overnight. Anesthesia was induced and maintained with intra-

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Table 1. Laboratory Data during Liver Transplantation in 12 Dogs

Variable	Preanhepatic stage		Anhepatic stage		Postanhepatic stage	
	I + 30 min	II - 5 min	II + 5 min	III - 5 min	III + 5 min	III + 30 min
Body temperature (°C)	36.0 ± 0.3	35.1 ± 0.2 ^a	34.2 ± 0.3 ^a	33.7 ± 0.3 ^a	32.9 ± 0.4 ^{a,b}	32.8 ± 0.4 ^{a,b}
Arterial blood						
Hematocrit (%)	44.3 ± 1.6	42.4 ± 1.8	34.2 ± 2.3 ^a	34.1 ± 1.7 ^a	28.5 ± 2.3 ^{a,b}	27.3 ± 1.9 ^{a,b}
pH	7.43 ± 0.02	7.43 ± 0.02	7.42 ± 0.02	7.34 ± 0.02 ^a	7.30 ± 0.02 ^{a,b}	7.23 ± 0.02 ^{a,b}
Paco ₂ (mm Hg)	29.3 ± 1.5	27.3 ± 1.2	25.0 ± 1.5 ^a	26.4 ± 1.8 ^a	24.6 ± 1.5 ^{a,b}	26.5 ± 2.0 ^a
Pao ₂ (mm Hg)	141.1 ± 11.5	147.7 ± 12.1	148.4 ± 7.0	148.8 ± 6.7	154.7 ± 7.6 ^{a,b}	154.9 ± 9.5 ^{a,b}
Base deficit	3.7 ± 0.7	4.3 ± 0.6	6.3 ± 0.6 ^a	9.7 ± 0.8 ^a	12.8 ± 0.8 ^{a,b}	14.8 ± 0.8 ^{a,b}
Na (meq/L)	146.7 ± 0.8	146.3 ± 1.1	142.1 ± 0.8 ^{a,b}	144.4 ± 1.4 ^a	141.6 ± 1.3 ^{a,b}	142.2 ± 1.3 ^a
K (meq/L)	2.53 ± 0.08	2.60 ± 0.12	2.81 ± 0.10 ^a	2.78 ± 0.08 ^a	4.10 ± 0.27 ^{a,b}	3.30 ± 0.20 ^{a,b}
Hepatic venous blood						
pH	7.42 ± 0.02	7.40 ± 0.02	—	—	7.15 ± 0.03 ^{a,c}	7.14 ± 0.04 ^{a,c}
PvCO ₂ (mm Hg)	32.2 ± 1.4 ^a	32.5 ± 1.8 ^a	—	—	44.2 ± 2.8 ^{a,c}	44.5 ± 3.8 ^{a,c}
PvO ₂ (mm Hg)	57.8 ± 6.3 ^a	43.8 ± 2.0 ^{a,c}	—	—	21.4 ± 2.2 ^{a,c}	26.0 ± 3.2 ^{a,c}
Base deficit	3.3 ± 0.6	3.8 ± 0.5	—	—	12.4 ± 1.1 ^a	12.8 ± 1.3 ^{a,c}
Na (meq/L)	147.0 ± 0.9	145.5 ± 1.1 ^a	—	—	140.9 ± 1.1 ^a	143.2 ± 1.2 ^a
K (meq/L)	2.63 ± 0.14	2.87 ± 0.23 ^a	—	—	4.92 ± 0.50 ^{a,c}	3.60 ± 0.26 ^{a,c}

Values are mean ± SEM.

^aDifferent from the values at I + 30 min.^bDifferent from the values at III - 5 min.^cDifferent from the corresponding values in arterial blood.

venous ketamine (2 mg/kg followed by 1 mg/kg every 20–30 min), plus pancuronium bromide for muscle relaxation. The dogs were mechanically ventilated with F_IO₂ of 0.3 and end-tidal CO₂ was maintained between 4 and 5%. Femoral arterial and jugular venous catheters were inserted for blood sampling and monitoring of arterial and central venous pressures. Crystalloid solution without glucose (Plasma-Lyte A, Travenol Laboratories, Inc., Deerfield, IL) was infused at a rate of 40 ml·kg⁻¹·hr⁻¹. Dopamine was infused to maintain mean arterial pressure above 70 torr. The surgical technique has been reported elsewhere (6). Surgery in the donor and recipient was synchronized to minimize donor organ ischemic time. The operation has three stages: a preanhepatic stage (stage I), from the induction of anesthesia to hepatectomy; an anhepatic stage (stage II), from hepatectomy to reperfusion of the graft; and a postanhepatic stage (stage III), from reperfusion of the graft liver to the end of surgery. The donor organs were preserved with cold (0–4°C) lactated Ringer's solution. In all recipient dogs, venous bypass (Bio-Medicus, Inc., Minnetonka, MN) was used during the anhepatic stage of surgery to divert blood from the splenic and femoral veins to the jugular vein. The graft liver was reperfused by unclamping the portal vein and the supra- and infrahepatic inferior vena cava after the vascular anastomoses were completed. Throughout the procedure, no glucose was administered to the recipient dogs: Neither the administered electrolyte solution nor the

organ preservation solution contained glucose, and no blood was transfused during the study.

In the preanhepatic stage, femoral arterial and hepatic venous blood samples were drawn 30 min after laparotomy (I + 30 min) and 5 min before the beginning of the anhepatic stage (II - 5 min). Hepatic venous blood samples were taken by venipunctures at the proximal part of the hepatic vein to avoid contamination by blood from the inferior vena cava. During the anhepatic stage, arterial blood was sampled 5 min after onset (II + 5 min) and 5 min before reperfusion of the graft liver (III - 5 min). In the postanhepatic stage, arterial and hepatic venous blood samples were collected 5 min (III + 5 min) and 30 min (III + 30 min) after reperfusion of the graft liver. The blood samples were analyzed to determine glucose levels, arterial blood-gas tensions and acid-base state, hematocrit, and levels of Na and K. Blood glucose levels were determined using the glucose oxidase test (YSI model 23 A glucose analyzer, Yellow Springs Instruments Co., Yellow Springs, OH). Arterial insulin and glucagon levels were measured in five animals during the preanhepatic and postanhepatic stages using radioimmunoassay technique (Serono Diagnostics, Braintree, MA). Data are reported as mean ± SEM. Data were analyzed by analysis of variance for repeated measures (ANOVA), and specific differences were assessed with the Student-Newman-Keuls test; *P* < 0.05 was considered statistically significant.

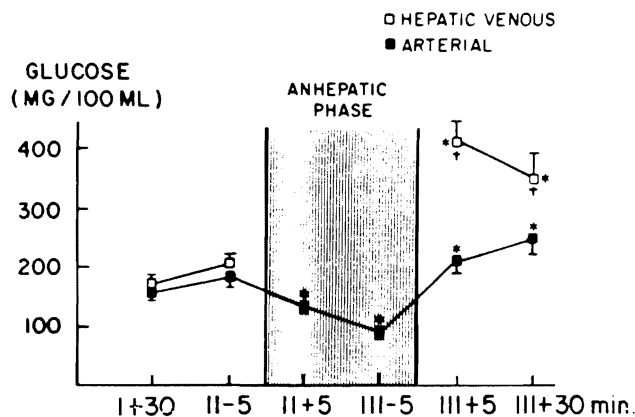


Figure 1. Blood glucose levels in arterial and hepatic venous blood during liver transplantation in 12 dogs. (Values are mean \pm SEM.) (*) Different from the values in the preanhepatic stage. (+) Different from the corresponding values in arterial blood.

Results

The preanhepatic stage lasted 78 ± 19 min, the anhepatic stage 47.5 ± 17 min, and the postanhepatic stage 92 ± 24 min. Intraoperatively, cardiovascular function was relatively stable except during the second half of the anhepatic stage and the first 15 min after reperfusion. Dopamine was infused in all animals to maintain mean arterial pressure above 70 mm Hg during the unstable period, the dose ranging from 5 to $20 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Laboratory data are shown in Table 1. All variables were within the normal range and stable in the preanhepatic stage. During the anhepatic stage, body temperature, hematocrit, and pH decreased. Reperfusion of the grafted liver caused a further decrease in body temperature, hematocrit, and pH. Similar changes occurred in hepatic venous blood after reperfusion, although hepatic venous blood was significantly more acidotic and had a higher potassium concentration than arterial blood.

Intraoperative blood glucose levels are presented in Figure 1. During the preanhepatic stage (stage I), arterial glucose levels were 161 ± 12 and 183 ± 16 mg/dl, and hepatic venous glucose levels were 170 ± 12 and 202 ± 15 mg/dl. The latter were slightly higher, but not significantly so. During the anhepatic stage (stage II), mean blood glucose levels decreased progressively to 135 ± 9 mg/dl after initiation of the anhepatic stage ($P < 0.05$), and to 88 ± 8 mg/dl immediately before reperfusion of the graft liver ($P < 0.05$). Blood glucose levels were between 60 and 70 mg/dl in three animals and 70 and 80 mg/dl in four animals at the end of the anhepatic stage. Blood glu-

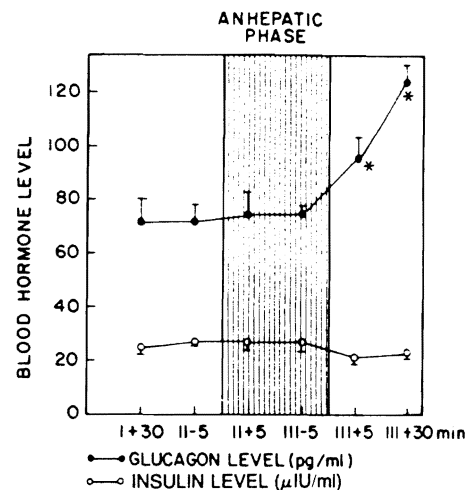


Figure 2. Arterial blood levels of glucagon and insulin during liver transplantation in five dogs. (Values are mean \pm SEM.) (*) Different from the values in the preanhepatic and anhepatic stages.

ucose levels, increased with reperfusion of the graft liver (stage III), were significantly higher in hepatic venous blood than in arterial blood: 206 ± 17 mg/dl at III + 5 min and 240 ± 24 mg/dl at III + 30 min in arterial blood, and 405 ± 37 mg/dl at III + 5 min and 346 ± 41 mg/dl at III + 30 min in hepatic venous blood. Plasma insulin levels, initially $24.3 \pm 1.0 \mu\text{IU/ml}$, did not change significantly during the entire observation period (Fig. 2). Plasma glucagon levels did not change during the preanhepatic or anhepatic stage (71.3 ± 20.5 and 73.9 ± 27.4 pg/ml, respectively) but increased steadily after reperfusion of the graft liver, reaching peak 30 min after reperfusion (123.5 ± 33.6 pg/ml), significantly above preanhepatic and anhepatic levels. In five animals blood glucose levels were compared with the glucagon/insulin ratios, but the correlation was very poor ($r^2 = 0.02$). On completion of the study, all dogs were transfused with whole blood obtained from the organ donor dogs; ten animals received 2 units and two animals received 3 units. Two animals died of pulmonary edema and pneumothorax at the end of surgery. Three animals died postoperatively within 48 hr and seven animals lived more than 6 postoperative days.

Discussion

The liver is responsible for uptake, storage, and release of glucose, and for gluconeogenesis. The blood level of glucose is determined by the balance between

release of glucose into the blood stream and glucose utilization by the body. These are influenced by, among other factors, the activities of insulin, glucagon, catecholamines, and glucocorticoids. Hepatic uptake of glucose and glycogen synthesis are enhanced by insulin. Glucagon stimulates gluconeogenesis and glycogenolysis and thereby increases hepatic output of glucose. Secretion of glucagon, epinephrine, and growth hormone can increase in response to hypoglycemia and stress. The liver is exposed to high concentrations of insulin and other hormones in portal blood, and the effects of these hormones on hepatic glucose metabolism may be more important than has been recognized. Because of the major role of the liver in glucose homeostasis, significant changes in blood glucose levels are expected during liver transplantation in experimental animals and in patients.

In the animals studied, exogenous glucose administration, including that in blood transfusions, was completely avoided. The dogs had normal preoperative hematocrits, and blood loss during surgery was minimal until the postanhepatic stage, so transfusion could be delayed until the study was completed (30 min after reperfusion). In the preanhepatic stage, glucose levels were stable, and arterial and hepatic venous blood glucose levels were similar, but initiation of venous bypass decreased hematocrit and blood glucose levels significantly. These decreases were most likely due to hemodilution from the priming solution in the bypass system, 250 ml balanced electrolyte solution. As the anhepatic stage progressed, blood glucose levels decreased further, possibly owing to continuing glucose utilization with decreased glucose production. In the present study the mean duration of the anhepatic stage was 47.5 min, about one-half the 93 min reported in clinical cases (7). With a longer anhepatic stage, glucose levels may decrease further in animals. Plasma insulin and glucagon levels did not change during the preanhepatic and anhepatic stages. Although blood glucose levels decreased during the anhepatic stage, the levels may not have been low enough to cause glucagon release.

The changes in metabolic variables with reperfusion are similar to results obtained during human liver transplantation: metabolic acidosis, hyperkalemia, hemodilution, and hypothermia caused by the release of cold, hyperkalemic, acidotic fluid from the graft liver (8-10). Reperfusion of the liver significantly increased arterial blood glucose levels. The increase may have been secondary to a massive release of glucose from the newly implanted liver, as indicated by the higher glucose level in hepatic venous blood compared with that in arterial blood and by the association

of the increasing arterial glucose level with the decreasing hepatic venous glucose level. A similar observation has been made by Halliday et al., who demonstrated progressively increasing glucose levels in the hepatic venous blood of the continuously perfused pig donor liver (11). Ischemic injury in the hepatocytes may have damaged cell membrane permeability, which allowed the release of intracellular glucose (12). It is interesting to note that plasma glucagon levels progressively increased after reperfusion despite arterial hyperglycemia. The increase in glucagon levels may have been caused by delayed release of glucagon in response to a low blood sugar level during the anhepatic stage or, alternatively, the release of glucagon may have played a role in the postreperfusion arterial hyperglycemia. However, a positive relationship between blood glucose levels and glucagon/insulin ratios was not seen in this study, although the lack of correlation could be due to the small number of animals studied. The administration of dopamine could have increased the secretion of glucagon, but only minimally. Thus, sudden hyperglycemia, especially in hepatic venous blood, that occurred within 5 min after reperfusion is unlikely to be hormonal in origin. Hypothermia in the recipient dogs could have decreased glucose utilization, and the relative ischemia of the donor liver occurring after reperfusion may also have affected the graft liver's sensitivity to hormones and intracellular enzymes responsible for glycogenolysis. This study was limited to 30 min after reperfusion; glucose metabolism in the postoperative period requires further investigation. It is also unknown whether or not the amount of glucose released from the reperfused graft liver has any prognostic value with respect to functional recovery of the organ, if postreperfusion hyperglycemia were caused by ischemic damage of the donor liver.

Similar changes in glucose homeostasis are expected to be seen in patients receiving liver transplants, although there are several differences between our experimental design and clinical patient care. In the animals studied, anesthesia was maintained with ketamine, which could have increased blood glucose level indirectly by releasing catecholamines (13), and the duration of the anhepatic stage was shorter than that in patients, which might have led to the higher glucose level than the values expected in patients. However, hyperglycemia is more likely to occur in patients undergoing liver transplantation. Glucose metabolism is altered in patients with chronic liver disease, and high levels of circulating insulin are common owing to hypersecretion of insulin or inadequate hepatic clearance of insulin (14), but these patients

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are known to be resistant to insulin action (15). A high plasma glucagon level is frequently observed, caused by hypersecretion and the effects of portasystemic shunting (16). Clinically, glucose intolerance and higher than normal blood glucose levels are not unusual. In patients, the intraoperative transfusion of blood preserved in dextrose solution (CPDA-1), which contains 200 mg/dl of glucose, is unavoidable, and flushing of preservation solution (Collins' solution, glucose 3.75%) into the systemic circulation may supply enough glucose to maintain adequate glucose levels. The high catecholamine levels observed in patients receiving liver transplants (Uram et al., unpublished data, 1984) may counteract the peripheral effects of insulin, and possible disturbances of the hormonal balance between insulin and glucagon may occur. Furthermore, the donor organ with a longer ischemic time in patients (4-8 hr) (1) may release more glucose on reperfusion, whereas, glucose utilization is decreased by frequent inadvertent hypothermia. The effects of postreperfusion hyperglycemia on urine output and its composition were not determined in the present study. Hyperglycemia exceeding the transport maximum of the renal tubules may cause glucosuria and osmotic diuresis.

In conclusion, this study showed minimal hypoglycemia during the anhepatic stage and hyperglycemia after reperfusion of the graft liver in healthy dogs undergoing liver transplantation without exogenous glucose administration. The postreperfusion hyperglycemia appears to be secondary to a release of glucose from the newly grafted liver. The results suggest that hypoglycemia is less likely in patients when glucose is administered by transfusion of banked blood, and hyperglycemia may occur if additional exogenous glucose is given, especially after reperfusion of the graft liver.

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