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Oxygen consumption predicts outcome in porcine partial liver grafts

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ABSTRACT

Background: High oxygen consumption (OC) in recipients of cadaveric whole liver grafts is associated with a poor prognosis. The aim of this study is to investigate the relationship between intraoperative hepatic OC and graft function and survival in a porcine partial liver graft model.

Material and methods: Experiments followed the Guiding Principles in the Care and Use of Laboratory Animals. Fourteen female pigs, 46–69 kg, received liver allografts of 17%–39% liver volume and were followed for 14 d. We measured donor and recipient body weights, percentage graft weight and expressed it as a percentage of standard liver volume, cold ischemia time, hepatic artery flow (HAF), portal vein flow (PVF), graft volume at sacrifice, serum lactate, prothrombin time, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, albumin, total protein, alkaline phosphatase, total bilirubin, and recipient survival. OC was calculated as follows: OC (mL/100 g/min) = ([Hemoglobin {Hb} × 1.34 × SaO_2 + 0.003 × PaO_2] × HAF + [Hb × 1.34 × SpO_2 + 0.003 × PpO_2] × PVF − [Hb × 1.34 × SvO_2 + 0.003 × PvO_2] × [HAF + PVF])/graft weight (100 g), and animals were divided into two groups: low OC group (OC < 2.0 mL/100 g/min) and high OC group (OC ≥ 2.0 mL/100 g/min).

Results: In survival analysis, four of seven low OC recipients (57% [$n = 7$]) survived until the end of the study period compared with one of seven high OC recipients (14% [$n = 7$]). The low OC group had a significantly higher survival rate than that of the high OC group ($P = 0.041$). Low OC was associated with higher HAF (mL/100 g/min) after reperfusion compared with that of the high OC group, 29.0 ± 13.8 *versus* 16.0 ± 11.1 mean ± standard deviation; $P = 0.073$. Serum alkaline phosphatase and total bilirubin in the low OC group were significantly better than those of the high OC group. Serum lactate was comparable in both groups. Graft weight at the time of sacrifice in the low OC group tended to be higher than that in the high OC group, but not significantly ($P = 0.097$).

Conclusions: High intraoperative OC is associated with lower HAF, decreased graft function, and decreased survival in the porcine partial liver graft model.

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1. Introduction

Advances in organ preservation, surgical technique, and immunosuppressive therapy have resulted in improved outcomes after liver transplantation [1]. In spite of these recent improvements, primary nonfunction and graft dysfunction occur in 2%–4% [2,3] and 13%–36% of liver transplantation recipients [4,5], respectively. For this reason, we continue to search for early predictors of graft function.

Metabolic alterations in liver allografts have been reported to influence graft outcome [6–8]. Because oxygen cannot be stored intracellularly, oxygen consumption (OC) of the graft after reperfusion may be a predictor of graft function. In fact, association between high OC of liver grafts after reperfusion and poor prognosis have been reported in a small retrospective clinical study [9].

The present study is based on the hypothesis that intraoperative OC of the partial liver allograft is an early predictor of postoperative graft function. We investigated the relationship between intraoperative OC of the liver allograft and the postoperative graft function and survival in our model of porcine partial liver allografts.

2. Materials and methods

2.1. Equipment

Histidine–tryptophan–ketoglutarate solution was provided from Essential Pharmaceuticals (Newtown, PA) LLC. Histidine–tryptophan–ketoglutarate solution was stored at 4°C until use.

2.2. Animals

Fourteen outbred female pigs weighing 23.5 ± 6.7 kg (mean ± standard deviation) were used as donors, and 14 outbred female pigs weighing 58.3 ± 6.6 kg were used as recipients. An additional animal was used as a blood donor for each donor and recipient pair. Experiments were carried out in accordance with the National Institutes of Health guidelines for the Care and Use of Laboratory Animals. The protocol was approved by Cleveland Clinic Institutional Animal Care and Use committee.

2.3. Anesthesia

For 12 h before surgery, animals had access to water only. The animals were premedicated with 20 mg/kg of ketamine by intramuscular administration. Anesthesia was induced by intravenous administration of 5 mg/kg of thiopental followed by endotracheal intubation, and maintained with oxygen and isoflurane by positive pressure mechanical ventilation.

2.4. Donor operation

The donor operation was carried out as previously described [10,11]. An intravenous line was placed in the internal jugular vein for fluid administration and central venous pressure (CVP) monitoring. A carotid artery line was placed for mean artery pressure (MAP) monitoring and intraoperative arterial blood sampling. A 16 gauge, 70 cm catheter (Arrow Inc, Reading, PA) was introduced into the orifice of the hepatic veins *via* the internal jugular vein for hepatic vein pressure (HVP) monitoring and intraoperative hepatic vein blood sampling. A 4-mm coronary vessel cannula (Medtronic Inc, St. Paul, MN) was introduced into the portal vein *via* an anterior branch for portal vein pressure (PVP) monitoring and intraoperative portal blood sampling.

The technique for parenchymal resection was previously described [10]. The right lobe and portion of the right paramedian lobe were used as the partial liver graft. During the surgical procedure, CVP, MAP, HVP, PVP, hepatic artery blood flow (HAF), and portal vein blood flow (PVF) were measured. HAF and PVF were measured using a transit time ultrasound blood flow meter, 400 series T402 (Transonic Systems Inc, Ithaca, NY). A data acquisition system and PowerLab software (ADInstruments Inc, Colorado Springs, CO) were used to simultaneously record CVP, MAP, HVP, PVP, HAF, and PVF. Liver biopsies and blood samples from hepatic artery and portal vein were obtained before and after parenchymal resection.

2.5. Recipient operation

The recipient operation was carried out as previously described [10,11]. Central venous, carotid arterial, and hepatic vein lines were placed as described in the donor operation. After midline laparotomy and mobilization of the liver, the portal triad was dissected. Total hepatectomy was performed using venovenous bypass by a centrifugal pump (Bio-Medicus Inc, Eden Prairie, MN), interconnecting the left internal jugular, splenic vein, and femoral vein *via* Tygon tubing (Norton Industrial Plastics, Akron, OH; 16 or 18 Fr for the jugular vein and 22 or 24 Fr for the splenic vein). The bypass blood flow was maintained over 30 mL/kg/min, under conditions of systemic heparinization (50 U/kg). The hepatic artery and common bile duct were divided close to the liver, and the portal vein was clamped and divided. After clamping both the upper and lower inferior vena cava, the liver was excised. The partial liver grafts were orthotopically transplanted with vascular anastomoses including upper inferior vena cava, lower inferior vena cava, portal vein, and hepatic artery. The bile duct was reconstructed using an end-to-end anastomosis. Allogeneic blood transfusion was given as required. During the surgical procedure, CVP, MAP, HVP, PVP, HAF, and PVF were measured. Liver biopsies and blood samples were obtained at baseline in the normal liver, and in the transplanted liver at 10, 60, and 90 min after reperfusion. At the end of the procedure, a central venous line, a carotid artery line, and a portal vein line were tunneled subcutaneously to exit at the back of the neck. Chronic blood flow probes were left *in situ* to record HAF and PVF and tunneled subcutaneously to exit at the back.

2.6. Postoperative care and monitoring

Medications were administrated through the intravenous line, including 0.01 mg/kg of tacrolimus and 25 mg/kg of cefazolin twice daily for the study period, and 1–1.5 mg/kg of ketoprofen twice daily for 5 d, and then as needed.