Development of a Large Animal Model of Cirrhosis and Portal Hypertension Using Hepatic Transarterial Embolization: A Study in Swine

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ABSTRACT

Purpose: To develop a clinically relevant porcine model of liver cirrhosis with portal hypertension by means of hepatic transarterial embolization.

Materials and Methods: Institutional animal care and use committee approval was obtained for all experiments. Pigs received transcatheter arterial infusion of a 3:1 mixture of iodized oil and ethanol into the hepatic artery in volumes of 16 mL in group 1 (n = 4), 28 mL in group 2 (n = 4), and 40 mL in group 3 (n = 4) with intent of bilobar distribution. Hepatic venous pressure gradient (HVPG) measurement, liver function tests, and volumetry were performed at baseline, at 2 weeks, and before necropsy.

Results: Cirrhosis was successfully induced in three animals that received 16 mL of the embolic mixture and in all four animals that received 28 mL. The animals in the 40-mL group did not recover from the procedure and were euthanized within 48 h. Increases in HVPG after 6–8 weeks versus baseline reached statistical significance ($P < .05$). Correlation between degree of fibrosis and volume of embolic agent did not reach statistical significance, but there was a trend toward increased fibrosis in the 28-mL group compared with the 16-mL group.

Conclusions: Transcatheter hepatic arterial embolization can be used to create a reliable and reproducible porcine model of liver cirrhosis and portal hypertension.

ABBREVIATION

HVPG = hepatic venous pressure gradient

Cirrhosis is the most common nonneoplastic cause of death in patients with hepatobiliary and digestive disease, and is the ninth most frequent cause of death in the United States (1). Portal hypertension and liver cancer are feared complications of cirrhosis, with an associated 5-year mortality rate exceeding 50% (1–3). There are medications to slow or reverse progression of fibrosis, and interventional procedures that can mitigate the effects of portal hypertension. Animal models are needed to test and validate these approaches (4,5).

The animal models of liver cirrhosis currently available are created by using a variety of hepatotoxins, such as carbon tetrachloride. The animals most commonly used for such models are mice, rats, and rabbits (6–8). Although these small and medium-sized laboratory animals are well suited for pharmacologic studies, large animal models are required to optimally test imaging tools and percutaneous interventions. In addition, such models can be used as large-animal hepatocellular carcinoma models, given that these tumors mostly arise in background cirrhosis. Suitable large-animal models of cirrhosis are currently lacking. The models currently described in the literature require several

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Research for this study was supported in part by a grant from the John S. Dunn Research Foundation and by the National Institutes of Health through Support Grant CA016672 to M. D. Anderson Cancer Center.

None of the authors have identified a conflict of interest.

J Vasc Interv Radiol 2011; 22:1329–1334

DOI: 10.1016/j.jvir.2011.04.016

repeated applications of the hepatotoxins and long induction periods (7,9). In addition, none of these models report concomitant development of portal hypertension. Pavcnik et al (10) attempted a percutaneous transhepatic technique to induce portal hypertension in swine in an experiment with the use of polyvinyl alcohol particles, but the portal pressures always returned to baseline levels at 1-week follow-up studies.

The swine species is particularly advantageous in the creation of a large-animal model of cirrhosis because of the anatomic and physiologic similarities between the porcine and human liver (11,12). The use of hepatic arterial embolization with ethanol has previously been reported to produce severe hepatocellular damage by direct tissue toxicity, endothelial damage, and "sludging" of erythrocytes. The addition of iodized oil prolongs the contact time between the ethanol and the tissues and promotes a more homogenous distribution of the agents (13).

The purpose of the current study was to develop a suitable and reproducible large animal model of liver cirrhosis.

MATERIALS AND METHODS

Animal Care

The institutional animal care and use committee approved the current study. Animals were maintained in facilities approved by the Association for Assessment and Accreditation of Laboratory Animal Care and in accordance with current United States Department of Agriculture, Department of Health and Human Services, and National Institutes of Health regulations and standards.

Preprocedure Preparation

Twelve domestic pigs weighing a mean of 41.4 kg (range, 29.8–46.4 kg) were sedated with an intramuscular injection of a solution containing ketamine hydrochloride (15 mg/kg), acepromazine (0.15 mg/kg), and atropine sulfate (0.04 mg/kg). Anesthesia was then induced with isoflurane (5%) administered by a facemask. When anesthesia was established, an endotracheal tube was inserted and anesthesia was maintained with isoflurane (1.5%–3%) and oxygen (0.8 L/min). The animals were given intramuscular doses of 5 mg/kg of the antibiotic enrofloxacin (Baytril; Bayer Animal Health, Shawnee Mission, Kansas) before each procedure and once daily for 5 days after each procedure.

At baseline, 2 weeks, and immediately before necropsy, all animals underwent nonenhanced computed tomography imaging (HiSpeed Advantage; GE Medical Systems, Milwaukee, Wisconsin) in 5-mm slices of the liver. Animals were weighed before embolization and before necropsy. All experimental and control procedures were performed by experienced radiologists familiar with porcine hepatic vascular anatomy.

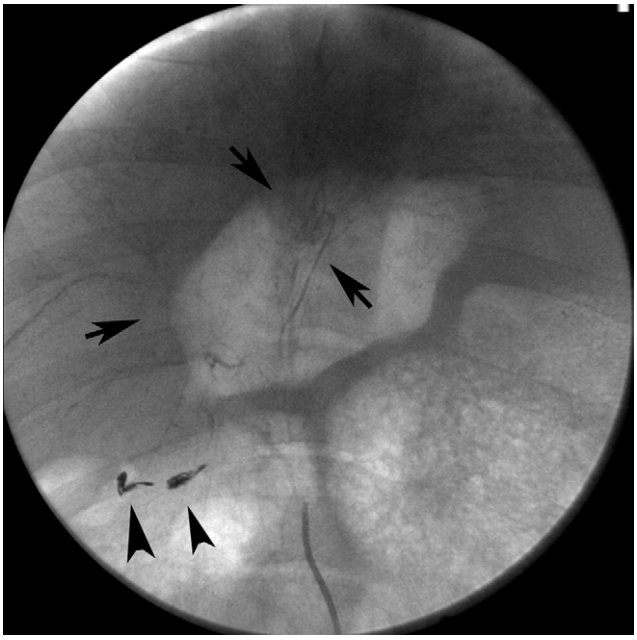

Figure 1. Transcatheter arterial hepatic embolization using ethanol/iodized oil mixture. Close-up of an anteroposterior radiograph of the abdomen in a later phase of the procedure shows embolic mixture in portal vein branches (arrows). Metallic coils are noted in the gastroduodenal artery (arrowheads). The coils are used to prevent nontarget embolization.

Hepatic Venous Pressure Measurement

A balloon-occlusion catheter was used to measure free and wedged hepatic venous pressures, and the hepatic venous pressure gradient (HVPG) was calculated according to the standards previously described by Pagan et al (14). Measurements were obtained at baseline before embolization, 2 weeks after embolization, and at 6–8 weeks before necropsy.

Transarterial Procedures

Access to the right common femoral artery was obtained by using Seldinger technique under sonographic guidance or via surgical cutdown. A single intravenous bolus of heparin (100 U/kg) was administered after vascular access was secure. A 5-F catheter (Sos-2; AngioDynamics, Queensbury, New York) was advanced over the wire into the aorta, and the celiac axis was selected. Celiac and hepatic digital subtraction angiography was accomplished by injecting iodinated radiographic contrast medium (meglumine diatrizoate; Nycomed, Zurich, Switzerland) through the catheter. A 3-F microcatheter (Tracker 325; Boston Scientific, Natick, Massachusetts) was then advanced coaxially into the common hepatic artery. Embolization of the gastroduodenal and right gastric arteries was then performed with metallic fibered coils. The microcatheter was advanced into the proper hepatic artery. Radiographic contrast medium was injected to confirm catheter position before embolization under fluoroscopy (**Fig 1**).

Three groups of pigs were randomly assigned to re-