The Use of the Woodchuck as an Animal Model for Evaluation of Transarterial Embolization

Luke R. Wilkins, MD, James R. Stone, MD, PhD, Jaime Mata, MS, PhD, Alisha Hawrylack, RT(R)(VI), Ewa Kubicka, MS, and David L. Brautigan, PhD

ABSTRACT

There are many shortcomings of current animal models as surrogates of hepatocellular carcinoma that handicap preclinical testing of embolization agents. The present study explores the feasibility of using the woodchuck (*Marmota monax*) as an animal model for the testing of novel embolization agents. Four woodchucks underwent magnetic resonance imaging, angiography, and left lobar hepatic artery particle embolization. Percutaneous access, arteriography, and lobar embolization were successful in all animals, with angiographic stasis obtained in the target vessel with minimal reflux of embolic material. These results support the feasibility of the woodchuck as an animal model for preclinical testing of embolization agents.

ABBREVIATIONS

FOV = field of view, HASTE = half-Fourier acquisition single-shot turbo spin-echo, HCC = hepatocellular carcinoma, PVA = polyvinyl alcohol, TE = echo time, TR = repetition time, WHV = woodchuck hepatitis virus

There has been much research into the optimal method of transarterial embolization of hepatocellular carcinoma (HCC). However, seeking methods to improve transarterial chemoembolization in a clinical setting is challenging given inherent research limitations (1). An alternative approach is to evaluate new embolization techniques or embolic materials in an animal model. Conversely, this approach presents a unique problem, as there are not only the usual set of requirements for a scientific study (eg. tumor is an appropriate analogue to human pathologic process, expense, ready reproducibility), but also the technical requirements necessary when considering the equipment involved in catheter-based intraarterial embolic agent delivery. In addition, in the clinical setting, chemoembolization is frequently performed in a segmental, subsegmental, or superselective fashion.

Commonly used HCC animal models are limited in their ability to serve as useful surrogates for catheter-based locoregional treatments. Currently available animal platforms for the study of HCC include the rat N1S1, rabbit VX2, and woodchuck hepatitis virus (WHV) models (1). The rat N1S1 orthotopically implanted tumor, although relatively inexpensive and readily reproducible, is not an accurate surrogate for testing transarterial embolization as a result of small arteries that are not amenable to catheterization for lobar embolization (1–3). The rabbit VX2 tumor, although it can be catheterized, is a non–hepatic-derived tumor and therefore not a suitable analogue to human pathologic processes (1,4,5). In contrast, the WHV woodchuck hepatoma model offers larger arterial size and a hepatic-derived tumor (1). WHV is closely related to human hepatitis B but does not incite cirrhosis and requires 1–4 years for tumor development after neonatal inoculation (6–8). The woodchuck model has primarily been used to investigate molecular biology and immunology of WHV (9,10) rather than testing treatments for HCC. The majority of HCC tumor-related research has centered on ablative technologies (11). The purpose of the present study was to show that access to the arterial supply of the woodchuck liver and delivery of embolic material is feasible and safe and replicates current clinical practice.

From the Department of Radiology and Medical Imaging (L.R.W., J.R.S., J.M., A.H.), University of Virginia Health Systems, Charlottesville, Virginia; and Department of Microbiology, Immunology, and Cancer Biology (E.K., D.L.B.), University of Virginia, Charlottesville, Virginia. Received January 11, 2017; final revision received April 4, 2017; accepted April 5, 2017. **Address correspondence to** L.R.W., Department of Radiology and Medical Imaging, University of Virginia Health Systems, 1215 Lee St., Box 800170, Charlottesville, VA 22908; E-mail: lrw6n@virginia.edu

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MATERIALS AND METHODS

Animal Care

All procedures were conducted according to international guidelines and were approved by the animal care and use committee. Four woodchucks (one male, three female; Northeastern Wildlife, Boise, Idaho) ranging in weight from 3.6 to 5.3 kg were used in this study. Free access to food and water was given until the night before angiography. Sedation was induced by ketamine 50 mg/kg, xylazine 5 mg/kg, and atropine 0.05 mg/kg, and endotracheal intubation performed. General anesthesia was maintained by ketamine dosing to effect. Vital parameters such as blood pressure, heart rate, and expired carbon dioxide levels were continuously recorded. The expired carbon dioxide levels were kept between 30 and 35 mm Hg. Immediately after the experiments, the animals were euthanized with an intravenous injection of pentobarbital.

Magnetic Resonance Imaging

Each animal underwent MR imaging on a 3-T Trio scanner (Siemens, Munich, Germany) with a 15-channel TX RX knee coil. MR imaging sequences included T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE) axial (200 × 153 field of view [FOV], 1.1 mm × 0.8 mm × 6 mm voxels, 450-ms repetition time [TR], 63-ms echo time [TE], one average, 0:11 acquisition time [TA]), T2-weighted axial fat-saturated HASTE (200 × 153 FOV, 1.1 × 0.8 × 6 voxels, 450-ms TR, 63-ms TE, one average, 0:11 TA), T2-weighted coronal HASTE (200 × 200 FOV, 1.0 × 0.8 × 4.0 voxels, 450-ms TR, 63-ms TE, one average, 0:11 TA), T1-weighted axial fat-saturated volumetric interpolated breath-hold examination (200 × 150 FOV, 1.0 × 0.8 × 2.0 voxels, 3.37-ms TR, 1.43-ms TE, one average, 0:22 TA), diffusion-weighted axial (260 × 221 FOV, 2.2 × 1.6 × 3.6 voxels, 4,000-ms TR, 78-ms TE, eight averages, 3:58 TA), T1-weighted volumetric interpolated breath-hold examination axial fat-saturated dynamic (four measurements with 12-s pause between measurements; 200 × 150 FOV, 1.0 × 0.8 × 2.0 voxels, 3.37-ms TR, 1.43-ms TE, one average, 2:04 TA), single-voxel liver spectroscopy (10 × 10 × 10 voxels, 1,690-ms TR, 67-ms TE, 20 averages, 0:37 TA), and 3D time-of-flight pre- and postcontrast arterial and venous phases with CARE Bolus tracking (280 × 192 FOV, 0.7 × 0.5 × 1.2 voxels, 3.18-ms TR, 1.25-ms TE, one average, 0:21 TA) with 1 mg/kg

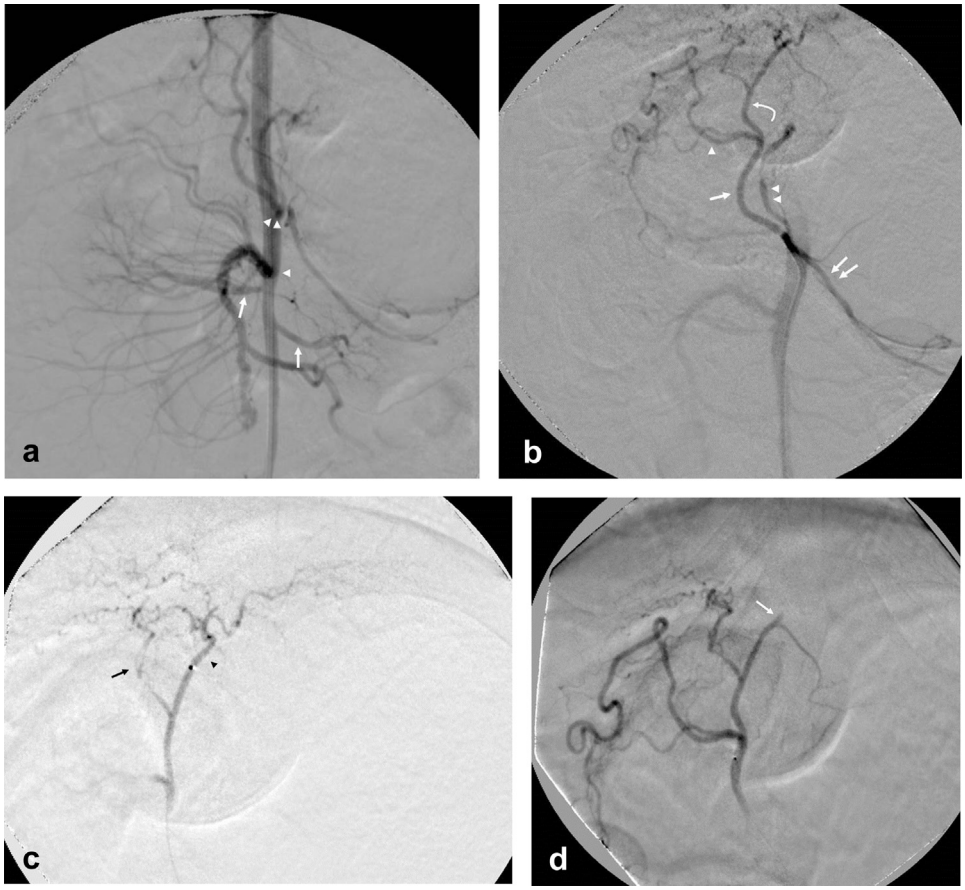

Figure 1. Selected arteriography images. **(a)** Abdominal arteriogram of the woodchuck shows a celiac artery (double arrowhead), superior mesenteric artery (arrowhead), and renal arteries (arrows). **(b)** Celiac arteriogram shows branching pattern of the celiac artery with splenic artery (double arrows), left gastric artery (double arrowhead), common hepatic artery (straight arrow), gastroduodenal artery (arrowhead), and proper hepatic artery (curved arrow). **(c)** Proper hepatic arteriogram shows right and left hepatic arteries (arrow and arrowhead, respectively). **(d)** Postembolization arteriogram shows occlusion of a segmental branch of the left hepatic artery (arrow).