Effectiveness of Endovascular Embolization with a Collagen-based Embolic Agent (Marsembol) in an Animal Model

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PURPOSE: To investigate in a porcine experimental model the effectiveness, tissue penetration, and histologic impact of renal artery embolization with a collagen-based nonadhesive embolic agent, marsembol.

MATERIALS AND METHODS: Fifteen pigs underwent embolization of one interlobular artery of the renal artery with collagen-resorcinol gel emulsified with Lipiodol and further polymerized with glutaraldehyde–formaldehyde mixture. Angiograms were obtained before, during, and after the procedure. Animals were euthanized at day 0 (n = 3), 1 week (n = 3), or 3 months (n = 7), and flat-panel three-dimensional rotational radiologic images of the kidneys were obtained. Arterial, medullary, and cortical samples were taken for histologic and scanning electron microscopic investigations.

RESULTS: Fifteen interlobular renal arteries were successfully embolized by delivering 1.7 mL ± 0.2 of the embolic agent. All the embolized arteries remained occluded at 3 months, leading to a major atrophy of the embolized portions of the kidneys. Imaging and histologic findings show that the embolic agent provided a distal vessel occlusion and entirely filled the lumen of the arteries up to the glomerular tufts. The homogeneous plug formed by the embolic agent induces very few inflammatory responses. The regenerative tubular processes were arrested at 3 months.

CONCLUSIONS: The collagen-based embolic agent described here has the properties required to perform embolization. These specific properties lead to very distal vessel embolization. The embolic agent is effective at 3 months in renal embolization.

J Vasc Interv Radiol 2010; 21:1419–1423

Abbreviations: GRF = gelatin-resorcin-formaldehyde, SEM = scanning electron microscopy

GELATIN-RESORCIN-FORMALDEHYDE (GRF)—sometimes called "French glue"—is used in cardiovascular surgery to seal aortic dissections (1–8). GRF, a polymer made of collagen polymerized with resorcin, glutaraldehyde, and formaldehyde, has never been used via the endovascular approach, primarily because it becomes solid after extemporaneous polymerization and also because it is not radiopaque. In the present study, we investigated the technical requirements for emulsifying GRF with Lipiodol ultrafluid contrast medium to make it radiopaque and prevent complete GRF solidification during the polymerization process. These modifications transformed GRF into an agent with the physical properties required to perform embolization through long, small-sized microcatheters (3 F). Thereafter, in our porcine experimental model of renal artery embolization, we investigated the effectiveness, tissue penetration, and histologic impact at 3 months of this collagen-based embolic agent (marsembol).

MATERIALS AND METHODS

Animals

The institutional Animal Care and Use Committee approved our experimental protocol. All animals were handled in accordance with the Guide for the Care and Use of Laboratory Animals. Fifteen pigs (initial body weight, 65 kg ± 3; age, 7 months; Blossin, Aubagne, France) were freely housed in facilities with natural daylight and free access to water for a 2-week acclimatizing period before treatment.

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None of the authors have identified a conflict of interest.

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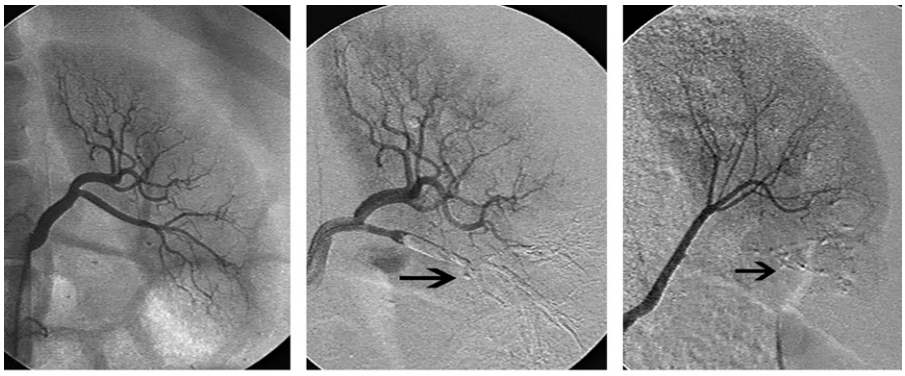
DOI: 10.1016/j.jvir.2010.04.026

Collagen-based Embolic Agent

From iterative attempts of mixing Lipiodol ultrafluid (ethyl esters of iodized fatty acids of poppyseed oil; Laboratoire Andre Guerbet, Roissy, France), the solidifying surgical glue GRF glutaraldehyde (Cardial, Saint-Etienne, France) was converted into the embolic agent in the following way: 2 mL Lipiodol and 0.5 mL gelatin were placed respectively in 5-mL syringes (Medallion; Merit Medical, South Jordan, Utah) connected by a three-way valve. The mixture was blended by stirring several times before addition of the polymerizing agent (0.1 mL glutaraldehyde–formaldehyde mixture). The final embolizing agent is obtained after stirring and leaving the product to stabilize for 10 minutes.



a. b. c.

Figure 1. Arteriograms before embolization **(a)**, immediately after embolization **(b)**, and at 3 months, before euthanasia **(c)**. Note the occlusion of the artery within the upper pole of the kidney in **b** and the persistence of occlusion of the artery in **c**.

Procedure

All procedures were performed on pigs anesthetized with intramuscular ketamine 15 mg/kg followed by intravenous infusion of midazolam (0.5 mg at 10 mL/min in isotonic Ringer lactate solution). Animals were placed in a dorsal recumbent position with their lower limbs folded down onto the table in the recommended radiologic posture (9). A digitized subtraction angiographic Stenoscop system (GE Medical Systems, Milwaukee, Wisconsin) was used for the radiologic procedures. Percutaneous access was obtained via Seldinger approach by puncturing the right superficial femoral artery under Doppler ultrasound guidance, and a 10-cm-long standard 5-F vascular sheath was introduced (Radiofocus; Terumo, Tokyo, Japan). Aseptic techniques were used throughout the procedure, and antibiotics (intravenous amoxicillin–clavulanic acid, 1 g/200 mg in 20 mL) were administered before and after the radiologic procedures. A 5-F (65-cm) angiographic UF catheter (Cordis, Miami, Florida) was advanced into the abdominal aorta over a 0.035-inch hydrophilic guide wire (Radiofocus; Terumo). An aortoiliac angiogram was obtained by injecting 25 mL of Hexabrix (Laboratoire Andre Guerbet) at 12 mL/sec. An interlobar artery of the left or right kidney was catheterized according to the routine procedure practiced in the radiology department and embolized with the embolic agent via a Rapid Transit microcatheter (Cordis). It took approximately 10 minutes ± 5 to achieve flow stasis in the artery; the quantity of embolic agent required to obtain complete embolization was 1.7 mL ± 0.2. The microcatheter was flushed with saline solution after use of the embolic agent. Digital angiograms were obtained before and after embolization on day 0 to check the procedure, and repeated 1 week later and before the animals were euthanized (at 3 months) to assess whether the vessels had become patent again. Routine blood counts and blood chemistry tests were performed when the agent was implanted and at each angiographic control examination. Animals were euthanized at day 0 ($n = 3$), 1 week ($n = 5$), or 3 months ($n = 7$) with midazolam 15 mg and chlorpromazine 25 mg in KCl 15% 20 mL by intravenous bolus. Immediately after euthanasia, the embolized kidney was surgically removed and then immersed in buffered 10% formalin liquid fixation medium for 2 days. The surgical specimens were investigated on a flat-panel three-dimensional rotational study (Innova 3100; GE Medical Systems) with multiplanar and volume-rendering reconstructions to study the renal parenchymal atrophy. The embolized renal areas were located under radiologic guidance and harvested in an identical manner for electron scanning microscopic (SEM) examination and conventional histology (9). A series of 5-μm orthogonal sections was cut from paraffin blocks and placed on slides for the pathology laboratory; the deparaffined slides were then stained with hematoxylin–eosin–safranine for microscopic observation (9).

RESULTS

The embolization of an interlobular renal artery and its runoff area was successfully achieved in each of the 15 animals included in this study (**Figs 1**,**2**). The embolizing agent was delivered at the origin of the renal interlobular branch artery and it spread spontaneously to the distal parts of the renal parenchyma. Embolization was considered to be complete when the agent had filled the whole arterial territory up to the distal end of the catheter. Because the embolizing agent was nonadhesive, the catheter was easy to withdraw in all cases, and there was no product sticking to the leading end of the microcatheter when it was removed. No embolization was observed outside the target areas. No passage of the embolic material to the venous system was noticed. The biologic and clinical follow-up of the animals did not reveal any toxic effect as a result of administration of the embolizing agent for the entire follow-up period (to a maximum of 3 months). The angiograms obtained before the animals were euthanized showed that the embolized areas remained occluded in all animals, as shown in **Figure 1**, at 3 months. The persistence of the radiopaque product inside the embolized area was also observed on the angiograms and confirmed by flat-panel three-dimensional rotational

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