Original Research

Fully MR-Guided Hepatic Artery Catheterization for Selective Drug Delivery: A Feasibility Study in Pigs

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Purpose: To demonstrate the feasibility of hepatic catheterization for selective delivery of therapeutic agents using a clinical MRI scanner for real-time image guidance.

Materials and Methods: Experiments were performed in three domestic pigs (70–80 kg) using a clinical 1.5-T MR scanner. After abdominal three-dimensional contrast-enhanced MR angiography (3D-CE-MRA) was performed, endovascular devices with susceptibility markers were tracked with passive tracking techniques. Catheters were maneuvered into the primary and secondary hepatic arteries. Selective catheterization was verified using selective time-resolved CE angiography. Paramagnetic microspheres were administered to a different region for each liver. The resulting biodistributions were investigated using MR images.

Results: Successful selective hepatic catheterization was repeatedly demonstrated using passive tracking techniques. 3D-CE-MRA significantly aided the interventional procedure by showing the vascular anatomy, and maximum-intensity projections (MIPs) were used as roadmaps during the interventions. In all cases, microspheres were successfully delivered to the selected regions. The catheters were visualized at a maximum frame rate of five frames per second, allowing a good depiction of the devices and a reliable catheterization of the hepatic arteries.

Conclusion: Fully MR-guided real-time navigation of endovascular devices permits complex procedures such as selective intra-arterial delivery of therapeutic agents to parts of the liver.

Key Words: passive tracking; interventional MRI; local drug delivery; liver treatment; hepatic catheterization


MINIMALLY INVASIVE endovascular treatment of liver malignancies (e.g., tumors and metastases) requires the intra-arterial delivery of therapeutic agents. Examples of endovascular treatment of the liver include selective chemotherapy (1), gene therapy (2), hepatic embolization, and selective internal radiation therapy (3,4). The success of these procedures requires accurate positioning of the catheter and imaging of the delivery and biodistribution of the therapeutic agents. X-ray fluoroscopy is currently the modality of choice for hepatic catheterization. However, in the past few years many efforts have been made to develop endovascular interventional MRI techniques to allow vascular interventions under MRI guidance (5–7). MR guidance of vascular interventions avoids the use of ionizing radiation and allows the exploitation of specific MRI features, such as adjustable high soft-tissue contrast and functional information (e.g., flow and perfusion). A hybrid setup of X-ray fluoroscopy and MR (X-MR) (1,8) allows the exploitation of MRI features while it maintains conventional catheter positioning under X-ray fluoroscopy. This approach is an important step toward introducing MRI-guided procedures in the clinic; however, several issues remain. A hybrid setup is rather expensive, X-MR-compatible equipment is required, and the patient is often moved from one imaging modality to the other during complex procedures such as local liver treatment or cardiac interventions. Therefore, it would be advantageous to perform a fully MR-guided procedure, particularly for applications that employ MRI for qualitative and quantitative evaluations of a therapeutic agent (9).

The aim of this study was to assess the feasibility of performing a fully MRI-guided endovascular catheterization of the hepatic arteries. For the MRI-guided endovascular intervention, “passive tracking” of the endovascular devices was exploited. This is a global detection (5) approach in which paramagnetic ring

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markers are mounted on the devices. The potential of fully MRI-guided intra-arterial local drug delivery is illustrated by selective deposition of paramagnetic microspheres to three separate regions: the territories supplied by the common hepatic artery, the right hepatic artery, and the left hepatic artery.

**MATERIALS AND METHODS**

**Endovascular Devices**

Conventional 5-F Cobra C2 (Glidecath; Cook) and 4-F Headhunter (Glidecath) catheters were magnetically prepared by mounting multiple paramagnetic ring markers (containing 0.8–1.5 mg Dysprosium oxide) to the tip segment at characteristic positions (Fig. 1a). A prototype MR-compatible guidewire was used. This guidewire consisted of a coated full-glass body (0.035 inch) and a short nitinol tip segment (20 cm) in which small paramagnetic markers were incorporated (Fig. 1b).

**MRI-Guided Intervention**

**Preparation Phase**

Experiments were performed on a clinical 1.5-T MR scanner (Gyrosan Intera, Philips Medical Systems, Best, The Netherlands). For the experiments, three domestic pigs (70–80 kg) were used. The animal experiments were performed with the approval of the local university animal care and use committee. During the experiments the pigs were under general anesthesia. After a 9-F sheath (Cordis, Roden, The Netherlands) was inserted into both common femoral arteries, the pigs were positioned inside the bore of the scanner. A wraparound body coil with four elements was used as the receive coil, which allowed accelerated acquisitions with sensitivity encoding (SENSE) techniques. Respiratory and electrocardiography (ECG) signals were acquired to allow triggering and gating to reduce motion and flow artifacts. Prior to the intervention, the abdominal vascular anatomy was imaged by intravenous injection of a contrast bolus (30 cc Gd-DTPA, Magnevist; Schering, Berlin, Germany), followed by high-resolution abdominal contrast-enhanced MR angiography (CE-MRA) during breath-hold (Table 1). The image data were acquired during the first arterial phase of the passing bolus. The position and orientation of the imaging planes for the tracking sequences were planned in the MR angiogram.

**Device Tracking**

The catheter and guidewire were inserted via the right femoral sheath. The guidewire protruded slightly beyond the catheter tip. A passive tracking sequence was used to visualize the paramagnetic markers (Table 1). For this and other gradient-echo sequences the bandwidth per pixel was at least 440 Hz. Reconstructed source, subtraction, and overlay images were presented to the interventionist using an in-room display. Markers were visualized during tracking using real-time subtraction images, which were merged with the corresponding maximum
intensity projection (MIP) of the 3D-MRA data set. This MIP served as a roadmap (10) during interventions. Subtraction was done by subtracting every incoming image from a baseline image (typically the fifth image). In this baseline image no devices were present in the field of view (FOV). During tracking there was no need to renew the baseline image because there was no shift of the anatomy. The subtraction images and MIP were merged in the following way: First the MIP was converted to a binary mask by thresholding. The subtraction images were blended with this binary mask by multiplication of the mask and subtraction images, followed by addition of the masked subtraction images to the mask. To reduce the severity of distracting subtraction artifacts in regions other than the vasculature, the roadmap was also widened by broadening the vasculature and used as a segmentation mask for the subtraction images. In this way the subtraction images were overlaid only in and slightly outside the vasculature, showing black markers on a white vasculature with a gray background. To qualitatively investigate the limits of marker visibility and acquisition speed, the parameters of the passive tracking sequence were varied. Echo time (TE) was varied between 4.7 and 9.2 msec, and slice thickness was varied between 30 mm and 50 mm. The other parameters varied were the SENSE acceleration factor (1.5 and 2.0), matrix size (1282), and segmented EPI (three readouts per excitation). The lower limit of the frame rate was regarded as the frame rate that hampered the detection of essential motion of the catheter tip. The upper limit of the frame rate was regarded as the frame rate at which the markers were lost too often because of decreased marker conspicuity.

**Catheterization and Selective Deposition of Microspheres**

Passive tracking techniques were used to navigate the catheters in the common hepatic artery or its branching vessels. To verify the position of the catheter, time-resolved selective angiography (Table 1) with a T1-shortening contrast agent (diluted (10%) Magnevist; Schering, Berlin, Germany) was applied (11–13). Then, to demonstrate the feasibility of local drug delivery to selected parts of the liver, a suspension containing paramagnetic microspheres was administered after selective catheterization was performed. The paramagnetic microspheres consisted of poly(L-lactic) acid, contained holmium (17% by weight), had a size distribution of 20–50 μm, and can be activated to perform internal radiation therapy of tumors (14). Half an hour before administration the microspheres were suspended in a saline solution that also included 1% Pluronic F68 (BASF, Ludwigshafen, Germany) and 10% ethanol (Merck, Darmstadt, Germany). Before administration of the microspheres, anatomic images were acquired (Table 1). In the first pig the catheter was positioned in the common hepatic artery, and 420 mg of microspheres were delivered to the complete liver. In the other two pigs smaller hepatic arteries (i.e., the left and right hepatic arteries) were entered. In the second pig 800 mg of microspheres were administered to the right lateral and medial lobes of the liver. For a human liver this globally corresponds to Couinaud segments 6–8. Finally, 450 mg of microspheres were administered to the left lateral lobe in the third pig (globally corresponding to Couinaud segments 2 and 4a). After administration of the microspheres, the catheter was flushed with 100 mL of saline, and the series of anatomical images was repeated (Table 1).

**RESULTS**

**Preparation Phase**

The preintervention MR angiograms gave clear representations of the abdominal arterial vasculature in three dimensions (Fig. 2). During the tracking experiments, selective reconstructions of the MR angiograms served as roadmaps.

**Device Tracking**

Qualitative evaluation of the images acquired with different acquisition parameters showed that the strong markers allowed a shorter TE and a reduced matrix size, which in turn allowed the frame rate of the tracking sequences to be increased. The use of EPI and SENSE further increased imaging speeds; however, these techniques also increased the noise level. Figure 3 shows a typical example of the image quality during interventions. For this example a frame rate of about two images per second was employed, which allowed an acceptable feedback during the interventions. In this study the most convenient compromise between the frame rate and image quality was found to be a low spatial (2.7 mm/pixel), high temporal (five frames/second) resolution tracking sequence with TE = 4.7 msec, TR = 9.6 msec, flip angle = 10°, EPI factor = 3, slice thickness = 30 mm, and no SENSE acceleration.

The tracking sequences used allowed real-time depiction of the catheter’s position. The visibility of the guidewire was sometimes unsatisfactory because the relatively weak markers on the guidewire were obscured at times by respiratory motion artifacts. Although the
markers on the catheters were also periodically obscured, this did not influence the success of the interventions. The tracking images revealed that the catheters were not fully MR-compatible, since a weak RF artifact was observed at the base of the catheters. This was most likely due to the light metal braiding of the conventional X-ray fluoroscopy devices.

**Catheterization**

The passive tracking sequences repeatedly allowed successful hepatic catheterization, even for the smaller arteries branching off the common hepatic artery (Fig. 4). The time required for superselective hepatic catheterization was about 10 minutes after the insertion of the devices. Most of this time was spent in superselective targeting, which required repeated verification and replacement of the catheter. The durations of the catheterizations of the hepatic arteries are given in Table 2. Repositioning of the device and verification of its position with the time-resolved angiography took approximately two minutes.

**Selective Deposition of Microspheres**

Correct catheter positioning was confirmed by enhancement of the intended region after injection of contrast agent. This enhancement also indicated the target area for selective deposition of the microspheres as depicted by the T$_2$*-weighted imaging (Table 1), as illustrated in Fig. 5.

**DISCUSSION**

We have demonstrated the feasibility of hepatic artery catheterization for selective delivery of therapeutics under full MRI guidance. MRI provided correct anatomical and vascular depiction, clear visualization of the devices, and accurate online feedback during navigation. This allowed the catheter to be positioned accurately and reliably. From our experience, we concluded that the three-dimensional nature of the acquired MRA data set greatly aided the intervention. The preoperative abdominal angiogram showed the vascular anatomy with high quality (contrast and resolution) in three dimensions, and selective projec-
tions could be made in any orientation to provide reliable roadmaps during the interventions. In practice, the CE acquisition can be replaced by other MR sequences (e.g., 3D phase contrast or balanced gradient-echo) with the ability to depict vascular anatomy; however, such alternative sequences may increase imaging time or depict veins as well.

The increased frame rate allowed easier catheter positioning during the tracking experiments as long as the markers remained visible and the signal-to-noise ratio (SNR) was acceptable. The highest achievable frame rate was about five frames/second, and for the markers employed in this study, higher frame rates resulted in unacceptable marker visibility and noise level. The ease of catheter positioning, however, is subjective, and acquaintance with the content and quality of the tracking images may significantly influence the personal quality requirements of the interventionist. Although the current image quality and frame rate were clearly sufficient for successful hepatic interventions, better catheter visualization may be desirable for easier catheterizations of smaller vessels, such as the smaller hepatic arteries. Although the current quality of tracking with MRI (i.e., device contrast, resolution, and frame rate) is apparently lower than that achieved with conventional X-ray fluoroscopy, it is expected that future developments in hardware (e.g., 3 Tesla magnets) and sequences will improve the image quality during MRI-guided catheterizations. The fact remains that interventionists who are currently used to the quality and convenience of conventional X-ray fluoroscopy will have to become familiar with both the limitations and advantages of endovascular interventional MRI. The main advantages are the adjustable and high soft-tissue contrast, the acquisition of functional information (e.g., flow and perfusion) during interventions, and the inherently noninvasive and three-dimensional nature of the technique, all of which facilitate accurate pre-, per-, and postoperative imaging.

A drawback of the employed passive tracking technique is its sensitivity to respiratory motion artifacts in the subtraction images. During tracking these subtraction artifacts periodically obscured the markers, and at
a few critical moments during the intervention (e.g., entering a branching artery) catheter movement was interrupted. Although this did not impede successful catheterizations, the quality of tracking will significantly improve if these subtraction artifacts are eliminated or reduced. Efforts are being made in other studies to reduce these kinds of artifacts (15,16).

Another drawback of the subtraction-and-overlay technique is that it may be necessary to update the roadmap if gross motion causes it to become less accurate. In that case a new roadmap should be acquired with either CE angiography or non-contrast-agent alternatives, such as 2D phase-encoded angiography or balanced gradient-echo techniques.

Before fully MR-guided catheterization can become a clinical reality, several challenges must be met. The most important challenge is the safety of the devices that are used. With the passive tracking approach, as employed in this study, catheters can be tracked safely because the use of long conducting structures is avoided. Recently this was also made possible for long transmission lines (17), which also allow the combination of active and passive methods—for example, by using a switchable susceptibility marker (18). This may be useful for cases in which one wants to avoid a disturbing overlap of the markers with the anatomy of interest. However, the catheters used in this study still contained a light metal braiding, since for this study the devices were chosen mainly with regard to their mechanical properties and hydrophilic coating, and the absence of a susceptibility artifact. From a manufacturing point of view, there should be no fundamental limitation in producing various types of MR-compatible catheters that have a predefined shape and favorable mechanical properties, and possess small paramagnetic ring markers. It is expected that if the production of MR-compatible catheters becomes attractive from a financial standpoint, the availability of MR-compatible devices will increase. With respect to the guidewire, more efforts must be made to obtain an MR-compatible wire that exhibits desirable mechanical properties. The tested prototype of the guidewire in this study is still undergoing development and was suboptimal, since the depiction of the markers incorporated in the tip was

**Table 2**

<table>
<thead>
<tr>
<th>Artery</th>
<th>Experiment 1</th>
<th>Experiment 2</th>
<th>Experiment 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common hepatic artery</td>
<td>1:55, 0:40</td>
<td>1:25, 2:40; 1:40</td>
<td>1:35</td>
</tr>
<tr>
<td>Right gastric artery</td>
<td>1:25</td>
<td>–</td>
<td>1:10</td>
</tr>
<tr>
<td>Gastroduodenal artery</td>
<td>1:20</td>
<td>–</td>
<td>1:20*</td>
</tr>
<tr>
<td>Right hepatic artery</td>
<td>2:25, 1:10</td>
<td>1:15</td>
<td>2:50, 1:40</td>
</tr>
<tr>
<td>Left hepatic artery</td>
<td>–</td>
<td>0:50, 0:35a</td>
<td>1:30, 1:00a</td>
</tr>
</tbody>
</table>

*Duration is given in (minutes:seconds) and rounded to 5 seconds.

*These durations had the common hepatic artery as a starting point.
insufficient and the mechanical properties differed from those of conventional guidewires. Again, it is expected that continued efforts will yield nonmetallic, safe guidewires with favorable mechanical properties and good MR visibility.

Another issue is that the feasibility of the proposed technique was tested under the controlled conditions of an animal experiment, and a routine clinical intervention might be more challenging. Our major reason for using an animal test was the safety of the current interventional devices. However, the presented experiments were essentially meant to give an indication of the visualization and tracking issues that might be encountered, and although the applicability of the present approach in the clinic remains to be assessed by a feasibility study in humans, we expect that the proposed techniques will allow for sufficient quality of tracking.

Selective hepatic catheterization was shown to be successful by selective time-resolved angiography and by the delivery of holmium-loaded microspheres. However, any other therapeutic substance could be injected, as long as the therapeutic agent has a distinct MR contrast label, is either positive (gadolinium chelates) or negative (iron oxides, etc), and its administration can be imaged during the intervention.

In conclusion, this study has shown that a fully MRI-guided endovascular hepatic intervention is feasible using a clinical 1.5-T scanner and devices with susceptibility markers. The advantage of a fully MRI-guided intervention is that it allows catheterization, exploitation of specific MRI features, and guidance and evaluation of therapy to be carried out with a single imaging modality.

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