Selective embolization with magnetized microbeads using magnetic resonance navigation in a controlled-flow liver model

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(Received 16 July 2018; revised 18 October 2018; accepted for publication 4 November 2018; published 17 December 2018)

Purpose: The purpose of this study was to demonstrate the feasibility of using a custom gradient sequence on an unmodified 3T magnetic resonance imaging (MRI) scanner to perform magnetic resonance navigation (MRN) by investigating the blood flow control method in vivo, reproducing the obtained rheology in a phantom mimicking porcine hepatic arterial anatomy, injecting magnetized microbead aggregates through an implantable catheter, and steering the aggregates across arterial bifurcations for selective tumor embolization.

Materials and Methods: In the first phase, arterial hepatic velocity was measured using cine phase-contrast imaging in seven pigs under free-flow conditions and controlled-flow conditions, whereby a balloon catheter is used to occlude arterial flow and saline is injected at different rates. Three of the seven pigs previously underwent selective lobe embolization to simulate a chemoembolization...
procedure. In the second phase, the measured in vivo controlled-flow velocities were approximately reproduced in a Y-shaped vascular bifurcation phantom by injecting saline at an average rate of 0.6 mL/s with a pulsatile component. Aggregates of 200-μm magnetized particles were steered toward the right or left hepatic branch using a 20-mT/m MRN gradient. The phantom was oriented at 0°, 45°, and 90° with respect to the B₀ magnetic field. The steering differences between left–right gradient and baseline were calculated using Fisher’s exact test. A theoretical model of the trajectory of the aggregate within the main phantom branch taking into account gravity, magnetic force, and hydrodynamic drag was also designed, solved, and validated against the experimental results to characterize the physical limitations of the method.

**Results:** At an injection rate of 0.5 mL/s, the average flow velocity decreased from 20 ± 15 to 8.4 ± 5.0 cm/s after occlusion in nonembolized pigs and from 13.6 ± 2.0 to 5.4 ± 3.0 cm/s in previously embolized pigs. The pulsatility index measured to be 1.7 ± 1.8 and 1.1 ± 0.1 for nonembolized and embolized pigs, respectively, decreased to 0.6 ± 0.4 and 0.7 ± 0.3 after occlusion. For MRN performed at each orientation, the left–right distribution of aggregates was 55%, 25%, and 75% on baseline and 100%, 100%, and 100% (P < 0.001, P = 0.003, P = 0.003) after the application of MRN, respectively. According to the theoretical model, the aggregate reaches a stable transverse position located toward the direction of the gradient at a distance equal to 5.8% of the radius away from the centerline within 0.11 s, at which point the aggregate will have transited through a longitudinal distance of 1.0 mm from its release position.

**Conclusion:** In this study, we showed that the use of a balloon catheter reduces arterial hepatic flow magnitude and variation with the aim to reduce steering failures caused by fast blood flow rates and low magnetic steering forces. A mathematical model confirmed that the reduced flow rate is low enough to maximize steering ratio. After reproducing the flow rate in a vascular bifurcation phantom, we demonstrated the feasibility of MRN after injection of microparticle aggregates through a dedicated injector. This work is an important step leading to MRN-based selective embolization techniques in humans. © 2018 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.13298]

Key words: hepatocellular carcinoma, magnetic resonance navigation, magnetized microparticles

**Abbreviations**

DEB drug-eluting beads  
MDEB magnetized drug-eluting beads  
MMP magnetized microparticles  
MRI magnetic resonance imaging  
MRN magnetic resonance navigation  
PC-MRI phase-contrast magnetic resonance imaging  
TACE transarterial chemoembolization

**1. INTRODUCTION**

Hepatocellular carcinoma (HCC) is the second cause of cancer-related mortality worldwide. Incidence rates have increased since the 1980s in North America. Transarterial chemoembolization (TACE) is the preferred treatment for intermediate stage HCC in patients with nonresectable tumors with preserved liver function. TACE requires selective catheterization and intra-arterial infusion of a suspension consisting of a chemotherapeutic agent combined with ethiodized oil and an embolic agent. This method extends life expectancy, although it is invasive and can thus only be repeated after several weeks. Intra-arterial chemotherapy through an injection port in the proper hepatic artery, which would allow a higher treatment frequency at a lower dose, has been proposed as an alternative treatment with promising results, but it lacks the ability for tumor targeting and it cannot be combined with embolization. In parallel, drug-eluting beads (DEBs) have been developed to combine local chemotherapy and embolization. DEB-TACE, which has been shown to be equally effective as conventional TACE, releases chemotherapeutic agents over a long duration, thereby extending the therapeutic effect. During TACE, the beads are injected superselectively into the tumor arterial feeders arising from the branch divisions of the hepatic artery through a catheter inserted by femoral or radial approach. Current limitations of conventional and DEB-TACE for liver tumors are: (a) lack of selective tumoral targeting after release from the catheter and the need for superselective catheterization, which is not always possible due in part to the difficult access to narrow feeder arteries using a microcatheter (53.3% eligibility in one instance); (b) potential damage to healthy liver due to nontargeted embolization; (c) poor visualization of tumor coverage after embolization; and (d) invasiveness of the procedure requiring superselective catheterization, repeated embolization sessions, exposure to ionizing radiation and iodine contrast and hospitalization for complications.

Magnetic actuation of magnetized MDEBs has been investigated with the objective of combining the high specificity of DEB-TACE, the minimal invasiveness of an implantable port and the slow drug release of DEBs. Magnetic
resonance navigation (MRN) has been proposed to steer magnetized particles using clinical MRI scanners. An embolization treatment based on MRN is designed to be performed as follows. At the preparation phase, a subcutaneous injection chamber is implanted in the patient’s subclavian artery, with an outlet catheter positioned in the proper hepatic artery. At the therapeutic phase, the patient is placed in an MRI, and multiple boluses of magnetized microbeads are successively injected through the chamber, with each bolus being magnetically steered in the segmental arteries feeding the tumor using a synchronized MRN sequence. Once all the aggregates have been injected and the patient is removed from the MRI, the magnetized microbeads, which are ferromagnetic, will disaggregate due to loss of magnetization. At that point, the microbeads, which are known to have the optimal size for HCC treatment, will be dragged by the hepatic arterial flow to the arterioles perfusing the target tumors, exactly as in a conventional DEB-TACE treatment. Due to the minimal invasive nature of the therapeutic phase, it can be repeated at an increased interval, thus potentially increasing survival. Additional advantages of this concept are the widespread availability of MRI scanners and using the imaging capabilities of MRI to identify the tumor, document particle distribution, and tumor coverage using the magnetic susceptibility artifact and residual tumor perfusion.

MRN has been successfully used to navigate a macrobead (1.5 mm) in the artery of a living pig using standard imaging gradient coils. Navigation across two vascular bifurcations was also possible with a 1-mm macrobead using an insert gradient coil and gradient magnitudes ranging between 24 and 64 mT/m. Recently, synchronization of steering and imaging sequences has been demonstrated for in vitro navigation of a 1-mm macrobead using imaging gradient coils in a clinical MRI scanner. 50-μm MDEBs were successfully navigated in vitro in a single-bifurcation system and in vivo in the left and right branches of the hepatic artery in a rabbit model with a magnetic gradient coil insert and a gradient magnitude of 280 mT/m with an acceptable degree of selectivity (70–80%). One technical limitation of those studies was the use of large beads, which possess higher magnetization but are not optimal for hepatic embolization. Currently available DEB size ranges between 70 and 300 μm which can be chosen depending on the target tumor vascularity. Another limitation was the use of magnetic gradient coil inserts which are more powerful than built-in imaging gradient coils but are not usable clinically due to their limited bore size. Prior studies also lack anatomical and physiological realism; they were either performed in nonbifurcating arteries or in nontubular channels with slow flow, which maximize steering efficiency due to the weakness of the magnetic force but that are not representative of physiologic rheological conditions. For a realistic MRN proof of concept, we first need to evaluate how to control the flow in large animal model. Then reproduce these controlled-flow conditions in vitro to evaluate steering efficiency. Furthermore, studies using small microbeads were performed with continuous injection of microbeads aggregates, an approach that is not compatible with particle navigation across two-branch divisions since steering gradients must be applied in a timely fashion to steer particles successively in different directions. An MR-compatible injector which can controllably form and release MDEBs aggregates has been proposed.

The first objective of this study was to determine if a slow laminar flow compatible with MRN could be achieved by occlusion of the proper hepatic artery with injection of saline distally to a balloon catheter in an animal model. The second objective was to assess the feasibility of MRN for selective embolization with magnetized microparticle (MMP) aggregates in a vascular phantom replicating physiological conditions.

2. MATERIALS AND METHODS

2.A. In vivo flow modulation and measurement

The protocol for this animal study was approved by the CHUM Research Center’s Institutional Animal Care Committee. During the experimentations, the pigs underwent general anesthesia and were euthanized at the end of the experiment.

All angiographic procedures were performed in an experimental angiography room (Artis Q, Siemens, Forchheim, Germany). At the start of the procedure, through femoral approach, the gastroduodenal artery and the left gastric artery (arising in the pig from the proper hepatic artery) were embolized with an experimental gel made of chitosan-sodium tetradecyl sulfate. Then, a 5-French compliant balloon catheter (Fogarty, Edwards Lifescience, Irvine, CA) was introduced in the proximal hepatic artery 3–4 cm below the right–left bifurcation. To evaluate the influence of selective liver embolization on the proximal hepatic flow, three pigs had selective particle embolization of the left medial lobe using a microcatheter (FasTracker 325, Boston Scientific, Marlborough, MA) advanced coaxially through the deflated balloon catheter. Experimental 50-μm radiopaque particles (ABK, Halifax, Nova Scotia) were injected until near stasis was obtained in the targeted lobe.

The pigs were then transferred to a 3T MR suite (Skyra, Siemens Medical Solutions, Erlangen, Germany). 3D magnetic resonance angiography centered on the abdominal aorta and liver was performed in the arterial phase using a T1-weighted gradient-recalled sequence with the following acquisition parameters: TR = 3.33 ms, TE = 1.23 ms, flip angle = 19°, and voxel size = 0.78 mm × 0.78 mm × 0.8 mm under breath hold after intravenous injection of 0.5 mmol/kg of gadolinium (Prohance, Bracco Imaging, Anjou, Quebec). 2D cine phase-contrast MRI (PC-MRI) was performed under cardiac gating in a plane perpendicular to the long axis of the main hepatic artery located 2 cm proximally to the bifurcation with the following parameters: TR = 24.4 ms, TE = 3.61 ms, flip angle = 20°, voxel size = 1.56 mm × 1.56 mm × 3.70 mm. The V_enc was set at the lowest value between 40, 60, and 80 cm/s for which no phase aliasing was visible (Fig. 1).
PC-MRI was performed in three conditions: using free flow and using controlled flow, either slow or fast. Controlled flow is defined as the condition whereby an occlusion balloon catheter is inflated in the proximal proper hepatic artery and 10 mL of a saline solution is injected distally to the occlusion point at either 0.5 mL/s (slow controlled flow) or 1.0 mL/s (fast controlled flow). The experimental conditions for each subject are given in Table I.

The corresponding mean, systolic, diastolic velocities, and the pulsatility indices were calculated for the different experimental conditions. The pulsatility index was calculated using Eq. (1):

\[ PI = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{time-averaged velocity}} \]  

This term represents the relative difference in systolic and diastolic velocities during the cardiac cycle.

### 2.B. In vitro MRN setup

To quantify navigation efficiency in realistic anatomical and physiological settings, we assembled a setup composed of an automated microbead aggregate injector, a glass Y-shaped hepatic arterial phantom, an MR-compatible camera, and a nonmodified clinical MRI scanner. The arterial phantom, shown on Fig. 2, has circular cross sections and dimensions matching approximately the diameter of the proper hepatic artery and its branch divisions in pigs (a 4-mm main branch and two 3-mm branch divisions angulated at 60°).

To perform MRN, a gradient sequence was programmed (IDEA, Siemens Medical Solutions, Erlangen, Germany). On execution, the sequence produced a constant gradient with magnitude 20 mT/m for 1–3 min per execution with the direction set to either left or right (at 90° relative to the main branch). The gradient coil amplifier temperature was monitored in real time by the operator from the console as a hardware safety precaution.

The phantom was positioned flat on the table at the center of the MR bore; the main branch was initially positioned parallel to the main magnetic field using a compass and successively rotated at 45° and 90°. At each orientation, the gradient was either turned off or applied toward the left or the right. For each combination of the above parameters, 20 MMP aggregates were injected successively in the phantom through a 5-French straight tip catheter whose tip was positioned 3 cm proximally to the bifurcation. The MMP aggregate injector, described in a later section, was positioned on the table, 1 m away from the MRI bore entrance as shown on Fig. 3.

Flow inside the phantom had two components: the catheter flow, set at a 0.2-mL/s constant flow rate, and the bypass flow injected around the catheter, set at a 0.4-mL/s mean flow rate, so that the cumulative flow was close to the 0.5-mL/s \textit{in vivo} injection flow. In addition, the bypass flow was not constant, but oscillating with frequency 1 Hz and amplitude 0.4 mL to prevent aggregates from sticking to the vessel walls.24

The steering direction was determined visually using the camera positioned above the phantom. A video of MMP steering was acquired for each injection to assess left and right steering.

### Table I. Experimental conditions for each animal model subject

<table>
<thead>
<tr>
<th>Flow condition</th>
<th>Subject number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free flow</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Slow controlled flow (0.5 mL/s injection)</td>
<td>X X X X X</td>
</tr>
<tr>
<td>Fast controlled flow (1.0 mL/s injection)</td>
<td>X X X</td>
</tr>
</tbody>
</table>

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**Fig. 1.** PC-MRI of the proper hepatic artery (PHA) in a pig that previously underwent embolization of the right medial lobe. (a) Magnitude axial oblique image showing the proper hepatic artery. (b) Corresponding phase image. Grayscale amplitude is proportional to flow, where white indicates high forward flow, black is high backward flow, and gray is null flow. (c) Coronal angiographic image in the arterial phase showing the PC-MRI imaging plane.
right steering ratios and aggregate velocity was calculated using a Kalman filter-based object tracking algorithm under Matlab (The Mathworks, Natick, MA). We define left and right steering ratios as the ratios of aggregates taking the left and right branches.

2.C. Magnetized microparticles synthesis

The MMPs used in this experiment are composed of Fe$_3$O$_4$ nanoparticles embedded in a poly(lactic-co-glycolic acid) (PLGA) matrix in which a chemotherapeutic agent of choice can be infused. Their size was 200 ± 20 μm and their magnetization saturation value was 30 emu/g.$^{25}$

2.D. Automated MMP injector

The automated MMP aggregate injector works according to the following principle: a suspension of MMPs is first manually injected into a tube linked to the aggregate injector. Then, flow is circulating in this tube, pushing the MMPs inside an aggregation area inside the injector, where a magnet holds the MMPs in place. When the aggregate has reached a predetermined size as shown by an infrared optical sensor, the flow in the MMP suspension tube is stopped, the magnet is pulled away from the aggregation area, and the aggregate is pushed into the catheter by a fluid injection from a second tubing. This device was successfully used to controllably and reproducibly inject aggregates of 25 ± 6 MMPs.$^{22}$

2.E. Theoretical model for MRN

A mathematical model for MRN in a Y-shaped tube aligned with the magnetic field was developed to predict the aggregate’s trajectory as a function of the experimental parameters. The model, describing time evolution of the system under magnetic, gravitational, and Stokes’ drag forces, allowed the calculation of aggregate longitudinal velocity and distance to transversal stabilization. The equation of motion of the system was derived and solved numerically using the symbolic computing program Maple (Maplesoft, Waterloo, Ontario, Canada) to find the expected trajectory of the aggregate for different magnetic gradient magnitudes. The model is schematized in Fig. 4.

We first computed an equivalent hydrodynamic radius $r_H$, given by Eq. (2), under the assumption that the aggregate adopts a chain-shaped conformation in the magnetic field. This radius was taken to be equal to the radius of a bead with equal cross-sectional area as the chain made of $n$ microbeads of radius $r$. The viscous drag was assumed to be proportional to the cross-sectional area of $n$ beads composing this chain.

\[ r_H = r \sqrt{n} \]  

(2)

We calculated the equilibrium angle $\theta_{eq}$ of the aggregate with respect to the vertical axis as a function of gradient magnitude and expressed it as $y_{eq}$, the transversal equilibrium position projected on the horizontal plane. Equilibrium occurs when the vector sum of the magnetic force $F_{mag}$ and
gravitational force $F_{\text{grav}}$ is normal to the tube wall at an angle $\theta_{\text{eq}}$ given implicitly by Eq. (3).

$$\sin(\theta_{\text{eq}}) = \frac{F_{\text{mag}}}{\sqrt{F_{\text{mag}}^2 + F_{\text{grav}}^2}}$$  \hspace{1cm} (3)

Under the small-angle approximation (since $F_{\text{grav}} \gg F_{\text{mag}}$), and by substituting the forces by their value in terms of the aggregate parameters, we approximated $\theta_{\text{eq}}$ as given by Eq. (4). We simplified the equation by expressing $\theta_{\text{eq}}$ in terms of the magnetic moment of the aggregate $\mu$ such that $\mu = nV_{\text{bead}}M_{\text{bead}}$.

$$\theta_{\text{eq}} = \frac{n V_{\text{bead}} M_{\text{bead}} \nabla B}{\sqrt{n^2 V_{\text{bead}}^2 M_{\text{bead}}^2 \nabla^2 B^2 + m^2 g^2}}$$  \hspace{1cm} (4)

The variable $V_{\text{bead}}$ is the volume of a bead, $M_{\text{bead}}$ is the magnetic moment of a bead, $\nabla B$ is the magnetic gradient.

To produce a plot of the trajectory of the aggregate, this equation was solved numerically and the bolus transversal and longitudinal position was displayed on the horizontal plane, with worst-case scenario initial conditions $\theta_0 = \frac{\pi}{2} + \theta_{\text{eq}}$ and $\theta_0 = 0$, which correspond to the initial position of the aggregate at the wall opposite to the wall of the target branch. To derive the equation for the stabilization distance, we used the small-angle approximation, valid only when $\theta_0 \ll 1$. Unlike for the worst-case scenario described above for which the equation of motion was solved numerically, this requirement is valid for most realistic aggregate release positions since the catheter tip is placed at the tube center. The equation of motion resulting from this approximation is given by Eq. (10).

$$\ddot{\theta} + \frac{6 \pi \eta H}{m} \dot{\theta} + \frac{\sqrt{\mu^2 \nabla^2 B^2 + m^2 g^2}}{m(R-r)} = 0,$$  \hspace{1cm} (10)

This equation corresponds to a damped harmonic oscillator, whose known analytical solution is a sinus curve inscribed in a decreasing exponential envelope characterized by decay constant $\lambda$, which represents the inverse of the time
required for the envelope curve to decrease to a fraction 1/e of its initial value. The decay constant $\lambda$ is given by Eq. (11).

$$\lambda = \frac{3\pi \eta r_H}{m}.$$  
(11)

The amplitude of the curve reaches a fraction $e$ of its initial value after a time to stabilization given by (12).

$$t_{eq,e} = \frac{1}{\lambda} \ln(1/e) = \frac{m \ln(1/e)}{\lambda}.$$  
(12)

Since the aggregate was assumed to brush the wall at a constant distance $R - r$ from the center of the tube and since the flow profile is parabolic, we estimated that the aggregate travels along the tube at the same constant velocity $v$ as the flow at the same radial position $R - r$, which is given by Eq. (13)

$$v = 2v_{\text{mean}} \left( 1 - \frac{(R - r)^2}{R^2} \right) = \frac{2Q}{\pi R^2} \left( 1 - \frac{(R - r)^2}{R^2} \right).$$  
(13)

The variable $Q$ is the flow rate and $v_{\text{mean}}$ is the mean flow velocity in the tube cross section. By using the relation $x_{eq,e} = t_{eq,e}v$, we found the longitudinal position $x_{eq,e}$ given by Eq. (14), from the release position after which the curve reaches a fraction $e$ of its initial value.

$$x_{eq,e} = \frac{mv \ln(1/e)}{3\pi \eta r_H}.$$  
(14)

To evaluate these equations, we assumed that the MMP aggregate adopts a chain-like shape, where $n = 20$ MMPS of radius $r = 100 \mu m$ were aligned with the main magnetic field $B_0$, resulting in an aggregate of mass $m = 2.47 \times 10^{-7}$ kg and hydrodynamic radius approximated to be $r_H = 4.47 \times 10^{-4}$ m. We approximated a distance of 3 cm between the tip of the catheter and a vessel with a diameter of 4 mm. The fluid viscosity was estimated to be $\eta = 2.5 \times 10^{-5}$ kg/m-s, halfway between that of water at NTP and blood. In addition, the magnetic microbeads that we used have a volume magnetization of $M_{\text{part}} = 8.85 \times 10^4$ A/m. The magnetic gradient generated by the imaging gradient coil was $G = 20$ mT/m. This model assumed that the aggregates are in contact with the bottom of the vessel wall due to gravity and that the flow velocity inside the tube has a parabolic profile. The assumed injection flow rate was 0.6 mL/s, which corresponds to the average injection flow rate in the in vitro experiment.

2.F. Statistical analysis

Arterial flow in vivo was reported as mean ± standard deviation. Changes in mean flow velocity and pulsatility index in free flow and controlled flow were expressed as differences in observed values and percentages.

Steering ratio differences according to gradient orientation relative to $B_0$ (0°, 45°, 90°) and between right and left steering ratios were compared using Fisher’s exact test. After Bonferroni correction, the significance level was set to $P = 0.025$.

3. RESULTS

3.A. In vivo flow modulation and measurement

In vivo measurements of hepatic arterial average velocities and average pulsatility indices under different conditions are shown in Table II and in Fig. 5.

In nonembolized pigs, compared to free flow, the velocity decreased by 42% with fast controlled flow and by 59% with slow controlled flow. The pulsatility index decreased by 57% with fast controlled flow and by 64% with slow controlled flow.

In one-lobe embolized pigs, compared to free flow, the velocity increased by 4% with fast controlled flow and decreased by 60% with slow controlled flow. The pulsatility index decreased by 69% with fast controlled flow and by 38% with slow controlled flow.

3.B. In vitro MRN

The left and right steering ratios and efficiency values are listed in Table III. Sample trajectories recorded by the optical camera are shown in Fig. 6. For the navigation without steering gradient, 55%, 25%, and 75% of the aggregates took the right branch for the 0°, 45°, and 90° phantom angulations, respectively. As shown in Table III, we achieved perfect (100%) steering efficiency after the injection of 20 aggregates for all combinations of gradient directions (right or left) and phantom angulations relative to $B_0$.

At 0° relative to $B_0$, both right and left gradients led to different left–right steering ratios compared to the baseline (respectively $P = 0.001$ and $P < 0.001$, respectively). At 45°...

<table>
<thead>
<tr>
<th>Condition</th>
<th>Flow velocity (cm/s)</th>
<th>Systolic–diastolic flow difference (cm/s)</th>
<th>Pulsatility index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonembolized pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free flow</td>
<td>4</td>
<td>20 ± 15</td>
<td>1.7 ± 1.8</td>
</tr>
<tr>
<td>Fast controlled flow (1.0 mL/s injection)</td>
<td>2</td>
<td>12.0 ± 9.1</td>
<td>0.7 ± 0.4</td>
</tr>
<tr>
<td>Slow controlled flow (0.5 mL/s injection)</td>
<td>2</td>
<td>8.4 ± 5.0</td>
<td>0.6 ± 0.4</td>
</tr>
<tr>
<td>Embolized pigs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free flow</td>
<td>3</td>
<td>13.6 ± 2.0</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Fast controlled flow (1.0 mL/s injection)</td>
<td>1</td>
<td>14.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Slow controlled flow (0.5 mL/s injection)</td>
<td>3</td>
<td>5.4 ± 3.0</td>
<td>0.7 ± 0.3</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation.
relative to $B_0$, the right gradient led to a different left–right steering ratio compared to the baseline ($P < 0.001$), but not the left gradient ($P = 0.047$). At 90° relative to $B_0$, the left gradient led to different left–right steering ratios compared to the baseline ($P < 0.001$), but not the right gradient ($P = 0.047$). Regardless of gradient direction, steering efficiencies after the application of MRN are significantly different from baseline left–right distribution ($P < 0.001$, $P = 0.003$, $P = 0.003$ respectively).

Aggregate velocities as measured from the steering videos by software object tracking are displayed in Table IV. The measured aggregate velocities were oscillating at the same frequency as the vibrating flow, with average minimum and maximum velocities of 0 and 12.4 $\pm$ 0.5 mm/s, except for the gradient-right-45° and gradient-left-90° datasets, which had average minimum and maximum velocities of 1.6 $\pm$ 1.4 mm/s and 28 $\pm$ 21 mm/s.

Based on our numerical model, theoretical trajectory of an aggregate is shown in Fig. 7. In the worst-case scenario, which is expected to lead to the most unfavorable steering outcome, the aggregate is released at the leftmost position in the vessel cross section with the gradient pointed right. Assuming an injection flow of 0.6 mL/s, the aggregate was expected to travel at 9.3 mm/s in the main branch. The trajectory exhibits a short transverse oscillatory behavior before it reaches steady transverse position after 0.11 s. To reach this steady state position, the aggregate will have transited through a longitudinal distance of 1.0 mm from its release position. This time to equilibrium varies linearly with microbead density; however, it is independent of gradient magnitude. The steady transverse position has an approximately linear dependence on the gradient magnitude. A 20-mT/m gradient leads to a transverse equilibrium position equal to 5.8% of the radius away from the centerline; a 40-mT/m gradient, 11.5% of the radius away; a 100-mT/m gradient, 28% of the radius away.

4. DISCUSSION

In the first phase of the study, we found that the use of a balloon catheter inflated in the hepatic artery of nonembolized pigs, combined with a 0.5-mL/s or 1.0-mL/s steady flow injection, yielded a controlled flow with low average velocity. These low flows were adequately captured using PC-MRI, which validates its use to monitor flow during MRN. In addition, we confirmed in vivo that a balloon catheter decreases the pulsatility index in nonembolized pigs. This showed that it will be possible to estimate in vivo the transit time of MMP aggregates, which is crucial in the accurate application of successive gradients in a multifurcation arterial network. For pigs with one-lobe embolization, the same conclusions cannot be made since pulsatility index was higher for slow controlled flow as compared to high controlled flow and mean velocities were similar for free and fast controlled flow. This effect could be attributable to the adaptive vasodilation of distal arteries in response to a drop in small arteriole pressure induced by embolization. However, both mean velocity and pulsatility index were decreased from free flow to slow controlled flow, which is consistent with the trend observed in nonembolized models. In addition, for both embolized pigs at slow controlled flow, the mean

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**TABLE III. Steering results in phantom**

<table>
<thead>
<tr>
<th>Total steering number</th>
<th>Gradient direction</th>
<th>Gradient magnitude (mT/m)</th>
<th>Right steering number (%)</th>
<th>Left steering number (%)</th>
<th>Steering efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0° angle with $B_0$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 No gradient</td>
<td>0</td>
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<td>45° angle with $B_0$</td>
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<td>5 (25)</td>
<td>15 (75)</td>
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<tr>
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<tr>
<td>90° angle with $B_0$</td>
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</tr>
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<td>0</td>
<td>15 (75)</td>
<td>5 (25)</td>
<td>n/a</td>
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velocity and pulsatility index are similar to that of nonembolized pigs. This indicates that steering efficiency will be independent of embolization status at the first hepatic arterial bifurcation.

In the second phase of the study, we observed perfect aggregate steering in a phantom model simulating an anatomical bifurcation and controlled physiological flow conditions. We showed that steering efficiency was significantly different from injections without steering. We also observed that the left–right steering ratios in vitro in the absence of a steering gradient for angles 45° and 90° are different from the expected 50% baseline. However, this phenomenon does not limit the applicability of the method since perfect steering efficiency was achieved upon gradient application.

The measured aggregate velocities measured were similar and within a narrow range, except for datasets gradient-right-45° and gradient-left-90°. The null minimum velocity was attributed to the friction between the aggregates and the phantom, and the 12.4 ± 0.5 mm/s maximum velocity to the pulsatile flow exerting an upward force lifting the aggregate away from the phantom wall. This maximum velocity is consistent with the theoretically calculated value, which is evidence for the validity of the model. The two exceptions correspond to the datasets for which the baseline steering

<table>
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<th>Table IV. Aggregate velocity as measured optically</th>
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<tr>
<td>Gradient direction</td>
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<td>Angle relative to $B_0$</td>
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<td>Velocity range (mm/s)</td>
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<td>Mean velocity (mm/s)</td>
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ratio is significantly different from 50%. This suggests that the skewed baseline steering ratio is due to off-center catheter positioning.

Finally, the model predicted that the trajectory reaches equilibrium rapidly for any realistic choice of parameters. From the numerical calculations of aggregate trajectory, we conclude that gravity is the limiting factor for steering efficiency in a circular cross-sectional tube since it restricts the trajectory at equilibrium to lie close to the centerline. The gravitational pull could be exploited by purposely orienting the target bifurcation downward through appropriate patient positioning.

The next challenge to address before in vivo navigation will be the implementation of an aggregate injector-gradient sequence synchronization system. The gradient sequence needs to be synchronized such that gradients are activated toward the target branch only when the aggregate approaches a bifurcation, thus enabling successive, multibifurcation navigation. This will also allow the safe achievement of higher gradient magnitude by reducing the gradient activation time. Using the current gradient parameters, the amplifier coil temperature increased over the course of the experiment from 20 up to a maximum of 50°C. A further gradient magnitude increase is desirable to allow a wider range of injection flows but will lead to a higher heating rate. According to the manufacturer, reducing the activation time will allow reaching a 40-mT/m magnitude while remaining below the recommended temperature threshold. To synchronize the gradient activation, real-time information on aggregate position must be acquired, which can be done using a catheter equipped with distal bead capture and release system27 followed by predictive modeling or by aggregate tracking using MRI.19

Our study has a few limitations. First, we used a phantom with a single bifurcation whereas superselective liver embolization in TACE procedures requires reaching the second-degree bifurcation. Performing two-bifurcation navigation in the current setting is of a technical rather than physical nature and requires gradient-aggregate synchronization. Second, low aggregate velocity as measured in this study may lead to an unreasonably lengthy procedure in large animals and we thus need to investigate in the future high velocity injections. The short aggregate transversal stabilization time calculated is compatible with these higher velocities. Theoretical models exist to predict how many aggregates will be needed for one-lobe embolization,28 but in vivo MRN experiments are needed to give an accurate estimate on the time required for one-lobe embolization. Third, the efficacy of magnetic microbeads as an embolizing agent cannot be evaluated by the current study and, although it is expected to be equivalent to that of beads used for DEB-TACE, only in vivo MRN experiments will allow to answer this question.

5. CONCLUSIONS

In conclusion, we measured the flow velocity and pulsatility index in an in vivo porcine model and reproduced the flow characteristics of an in vitro model of hepatic artery bifurcation. We performed MRN using a dedicated MR injector and a standard imaging gradient coil. Our study shows that MRN is achievable under physiological conditions using arterial occlusion and saline injection, in a one-bifurcation phantom model simulating an anatomical bifurcation and physiological conditions in a clinical MRI scanner. The high arterial flow and systolic–diastolic variation are not compatible with MRN which relies on the small magnetic force generated by the imaging gradient coil to steer the particle aggregates in the targeted branch division. The proposed balloon catheter-based method of flow control is a potential candidate to bring these technologies to clinical application. Moreover, the MRN experiments performed in the present study demonstrated the feasibility of performing MRN on a human scale. Compared to conventional TACE which requires repeated catheterization, the proposed MRN technique, which was shown allow magnetized beads navigation through an arterial bifurcation, can theoretically increase the treatment frequency when used together with an implanted injection chamber and improve tumor targeting due to the advanced imaging capabilities of MRI. To evaluate the feasibility of this application in vivo, selective one-lobe embolization experiments using gradient steering of magnetized microbeads on porcine models are planned.

ACKNOWLEDGMENTS

We thank Maxime Gérard, Zinan He and the personnel of the animal core facility of the CRCHUM, who contributed to the in vivo experiments. We also thank Michel Gouin and Danielle Blain, technologists. This work was performed as a collaboration between École Polytechnique de Montréal, Université de Montréal, Centre de recherche du Centre hospitalier de l’Université de Montréal (CRCHUM), the University of British Columbia and Siemens Healthcare. Funding for this project was supported by a Collaborative Health Research Project grant (CHRP) from the Natural Sciences and Engineering Research Council of Canada and Canadian Institutes of Health Research (NSERC-CIHR, #478474-15). François Michaud is supported by a Master’s student scholarship from the Fonds de Recherche du Québec — Nature et Technologies (FRQNT #197315). An Tang is supported by a Chercheur-Bourier Junior 2 fund from the Fonds de Recherche du Québec en Santé and Fondation de l’association des radiologistes du Québec (FRQS-ARQ #34939).

CONFLICTS OF INTEREST

We declare that we have received a contribution from Siemens (Germany) in the form of complimentary service and assistance and one author (Gerald Moran) is a Siemens Healthineers employee.

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