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Resotran® meets MPI – clinically approved Ferucarbotran reintroduced: a major leap towards MPI in humans

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Abstract

MPI has been on a trajectory towards clinical application in humans for years. As scanners and techniques mature, clinical testing is effectively prohibited by the lack of a clinically approved tracer. This changes now by the reintroduction of a Ferucarbotran-based tracer into the market, Resotran®. Although initially intended for use in MRI, we tested Resotran® for its viability in MPI. The other Ferucarbotran-based tracer fit for MRI and MPI is Resovist®, which is well known and characterized but was discontinued years ago. We present initial data on the characterization of Resotran® in comparison to Resovist®.

I. Introduction

Magnetic Particle Imaging (MPI) offers a tracer-based radiation free imaging technology for various clinical applications [1, 2]. Apart from mastering the technology itself, the availability of a viable tracer is an absolute prerequisite for the introduction of MPI into clinical use. SPION-based contrast media originally intended for use in Magnetic Resonance Imaging (MRI) have been demonstrated to be viable tracers for MPI. Unfortunately, SPIONs have been abandoned and discontinued in Europe over a decade ago thus effectively preventing the development of MPI into a viable clinical application. This has been true up until recently, when Resotran® (b.e.imaging, Germany), a Ferucarbotran-based contrast agent, has been clinically approved for use in humans and is now commercially available.

In an initial short study, the characterization of Resotran® has been investigated in comparison to Resovist® (Bayer, Germany) with Magnetic Particle Spectroscopy (MPS) [3], Critical Offset Magnetic Particle Spectroscopy (COMPASS) [4] and within a human-sized MPI scanner (interventional MPI) [5].

II. Materials and methods

For characterization and initial testing of a novel tracer for MPI, the particle system has to be compared to a well-known tracer, e.g., Resovist®.

II.I. Tracer

Resovist® was a well-known contrast agent for MRI. By shortening both, T1 and T2 relaxation times and its biological properties to be excreted by cells with reticuloendothelial systems, it was perfectly fit for the detection and characterization of liver lesions even in cirrhosis.

The same is true for Resotran® but clinical data are lacking due to its novelty especially for MPI.

Resovist® is well characterized and has been shown to work quite well for MPI [8]. Although the average core diameter for both, Resovist® and Resotran® is similar at approximately 5.8 ± 2.5 nm, the hydrodynamic diameter for Resotran® is significantly less scattered at 57.4 ± 2.1 nm vs. 45-65 nm for Resovist®, effectively preventing aggregates. Additionally, lactid acid has been added to improve pH-stability and chemical matrix (data on Resotran® as disclosed by the manufacturer).

The iron concentration for both, Resovist® and Resotran®, is given at 28 mg/ml.

For comparison, a dilution series of both particle systems has been prepared with concentrations 1:10 (2.8 mg/ml), 1:20 (1.4 mg/ml), 1:40 (0.7 mg/ml), 1:80 (350 µg/ml), 1:160 (175 µg/ml), 1:320 (87.5 µg/ml), 1:640 (43.75 µg/ml), 1:1280 (21.88 µg/ml), 1:2560 (10.94 µg/ml), 1:5120 (5.47 µg/ml). The sample size is 50 µl liquid stored in 5 mm NMR glass tubes.

II.II. Magnetic Particle Spectroscopy (MPS)

MPS is used as a gold-standard screening method for pretesting the performance of tracer for imaging systems [3]. As it can be seen as a 0D imaging system, a particle system shows within an MPS device the maximum signal as higher harmonics of the excitation frequency, which is set to $f = 20$ kHz. That means, MPS is a tool for initial proving the signal performance of MPI tracers. The amplitude of the excitation field is about $H_{AC} = 20$ mT.

The acquired time signal is corrected against distortions from the receive hardware (receive-chain correction), digitalized and Fourier transformed for data evaluation, here extracting the magnitudes of the higher harmonics.

II.III. Critical Offset Magnetic Particle Spectroscopy (COMPASS)

A novel spectroscopic method is the COMPASS method [4]. In contrast MPS, it uses an additional static offset magnetic field H_{DC} to investigate the phase behavior in the vicinity of so-called critical points (CP). Each higher harmonic in the spectrum of the nonlinear magnetization response of magnetic material show crossing points of the real and imaginary parts in dependency of H_{AC} and H_{DC} defining the CPs. The amount and position of these critical points depends on the ratio of H_{AC} and H_{DC} and also the particle system itself, which makes COMPASS an ideal candidate to investigate differences from tracers (fingerprinting).

The excitation frequency is set to f_{AC}=20 kHz. The magnetic field strength H_{AC} is step-wise increased from 0.6 mT to 20 mT in 0.55 mT steps at a static offset field of H_{DC}=20 mT. The acquired data set consists of multiple MPS data sets with different H_{AC} values. Each data set has been processed individually extracting the phase evolution at a desired harmonic.

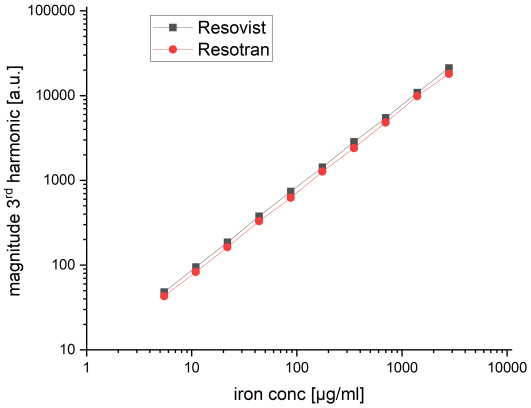

Figure 1: Results of a dilution series of Resovist® and Resotran®. Both tracers show the same linear signal behavior, but Resotran shows a 10% weaker signal strength.

II.IV. Human-sized MPI scanner

The interventional human-sized MPI scanner (iMPI) provides rapid projection imaging with a field of view (FOV) of about 20×25 cm² [5]. The generated field-free line (FFL) with a gradient strength of about 0.4 T/m is steered on a sinusoidal trajectory through the FOV with frequencies f_1=60 Hz and f_2=2,480 Hz. Each image has been acquired within 50 ms and reconstructed using image-based system matrix approach [6, 7]. The system matrix for the reconstruction has a size of 35×81 voxels with a distance of 3 mm covering a projection FOV of 10.5×24.3 cm². For reconstruction, an iterative Kaczmarz algorithm (100 iterations, λ=0.1) has been used.

III. Results and discussion

In Figure 1, the results for a dilution series of Resovist® and Resotran® is shown. The graph shows the amplitude of the 3^{rd} harmonic against the iron concentration. As expected, a linear behavior can be observed for both particle systems. The signal strength of Resotran® shows a 10% weaker signal in contrast to Reovist®.

Figure 2 shows the result of the COMPASS measurement. For both tracers, the phase evolution over increasing excitation field H_{AC} at a static offset magnetic field H_{DC} show identical behavior.

Figure 3 shows initial results of an undiluted Resotran® & Resovist® point sample within a human-sized MPI scanner [5]. Clearly a narrow point-spread-

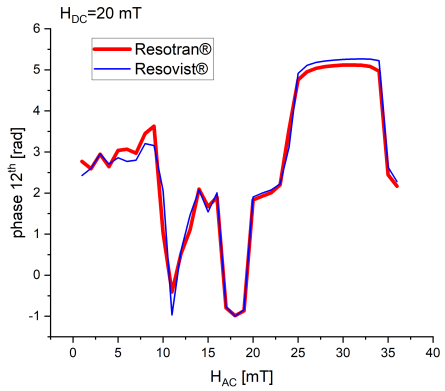

Figure 2: COMPASS Fingerprinting result of Resovist® and Resotran®. The phase evolution of both tracers shows identical behavior over increasing excitation field.

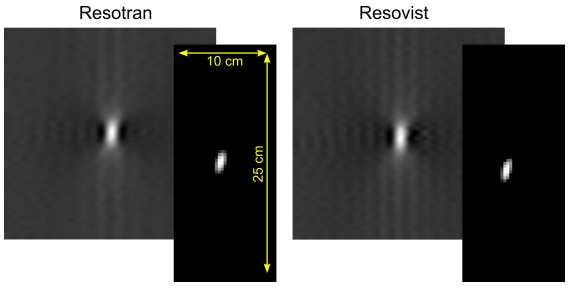

Figure 3: Raw-image of a point sample filled with undiluted Resotran® (left) and Resovist® (right) (point-spread function – PSF).

function (PSF) is visible, which provides a good spatial resolution capability. In addition, the reconstructed image is shown.

IV. Conclusions

Clinical studies to certify contrast media for use in humans are time-consuming and require significant financial resources. Although MPI is rapidly evolving, the community and commercial potential is still in its infancy so that the lack of a clinically approved tracer effectively prohibits MPI application in clinical scenarios. Fortunately, a Ferucarbotran-based SPIO, Resotran®, has become commercially available recently.

We characterize the signal properties of Resotran® in comparison to Resovist® with MPS, COMPASS and MPI. MPS reveals the signal strength of Resotran® is 10% weaker than for Resovist®. The COMPASS result shows a good agreement of the phase evolution. This means, that the basic particle structure seems to be identical.

A final MPI experiment demonstrates that Resotran® is a viable tracer for MPI. An initial PSF image shows similar results for spatial resolution.

As Resotran® was originally designed and approved for use in MRI, its availability and viability as tracer for MPI opens the way for future applications combining the potential of both technologies. Imaginably, the combination of the high temporal resolution of MPI for use in vascular interventions or perfusion imaging and the lesion characterization qualities of MRI with the same tracer becomes possible and actually would meet great demands in medicine.

As a first step towards MPI use in humans, future studies will explore the potential of iMPI in combination with Resotran®.

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Author's statement

Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent has been obtained from all individuals included in this study.

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