LETTER TO THE EDITOR

Three-dimensional real-time in vivo magnetic particle imaging

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Abstract
Magnetic particle imaging (MPI) is a new tomographic imaging method potentially capable of rapid 3D dynamic imaging of magnetic tracer materials. Until now, only dynamic 2D phantom experiments with high tracer concentrations have been demonstrated. In this letter, first in vivo 3D real-time MPI scans are presented revealing details of a beating mouse heart using a clinically approved concentration of a commercially available MRI contrast agent. A temporal resolution of 21.5 ms is achieved at a 3D field of view of $20.4 \times 12 \times 16.8$ mm$^3$ with a spatial resolution sufficient to resolve all heart chambers. With these abilities, MPI has taken a huge step toward medical application.

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Introduction

Over the last decades, tomographic imaging methods such as computed tomography (CT) (Ambrose 1973; Hounsfield 1973), magnetic resonance imaging (MRI) (Lauterbur 1973) and positron-emission tomography (PET) (Chesler et al 1973; Ter-Pogossian et al 1975) have become indispensable tools for the diagnosis of a large number of diseases. While PET provides high sensitivity in static imaging based on tracer materials, MRI and CT offer intrinsic tissue contrast at high spatial resolution and are capable of dynamic imaging. However, despite recent advances (Tsao et al 2003; Mistretta et al 2006), real-time imaging of 3D volumes using MR remains challenging. CT, as well as x-ray fluoroscopy, offers higher temporal resolution, but applies ionizing radiation.

Recently, a new imaging modality called magnetic particle imaging (MPI) has been presented (Gleich and Weizenecker 2005). It potentially offers quantitative 3D real-time imaging of ferromagnetic nano-particles at spatial resolutions comparable to established modalities. Therefore, it could become the modality of choice for diagnoses requiring
fast dynamic information, e.g., blood flow in the case of coronary artery disease. First demonstrations of the MPI technique on phantoms verified basic feasibility for static (Gleich and Weizenecker 2005) and dynamic 2D imaging (Gleich et al 2008), but high tracer concentrations were required due to low sensitivity. It remained unclear at that time, whether it would ever be possible to increase the sensitivity sufficiently to reach biocompatible tracer concentrations. Furthermore, evidence was missing, whether the tracer performance observed in the phantom fluid would reproduce in vivo.

In this letter, we show that, after major technical innovations, MPI is capable of 3D high-resolution real-time imaging of magnetic nano-particles flowing through the cardiovascular system of a living mouse. Using tracer concentrations in the range between 8 and 45 $\mu$mol (Fe) $l^{-1}$, we demonstrate that the sensitivity is already high enough for imaging clinically approved iron-oxide-based MRI contrast agents (Resovist, Bayer Schering Pharma) (Lawaczek et al 1997) at allowed concentrations below 40 $\mu$mol (Fe) $l^{-1}$.

A detailed description of the MPI principle has been published previously (Gleich and Weizenecker 2005). In brief, MPI requires ferromagnetic nano-particles, a static magnetic field (‘selection field’), an oscillating field (‘drive field’) and signal receive coils. The basic scanner setup is schematically shown in figure 1. The selection field provides a single field-free point in space (FFP), while it is non-zero at all other spatial positions. This field topology can be achieved using a Helmholtz-type coil setup supplied with opposite currents. In the close vicinity of the FFP, the orientation of the magnetization of the ferromagnetic nano-particles can easily align with an applied oscillating drive field, while at all other positions, it is forced to align with the local selection field direction. Since the particles have a nonlinear magnetization curve, the magnetization reorientation occurring around the FFP induces a signal in the receive coils at the drive field frequency $f_0$ and higher harmonics thereof. The signal is proportional to the concentration of particles at this position. If the FFP is moved over the object in a sufficiently dense trajectory, the local particle concentration can be imaged. For fast spatial encoding, the FFP can be moved using homogeneous oscillating fields. It turns out that a sufficiently large amplitude of the drive field induces a 1D FFP motion over the object,
enabling 1D spatial encoding. To encode three spatial directions, two additional orthogonal drive fields are necessary. If the respective drive frequencies differ only slightly, the FFP will follow a 3D Lissajous trajectory. The broadband acquisition of the signal generated by the changing particle magnetization under the influence of the FFP motion yields the MPI signal. From the information encoded in higher harmonics and mixtures of the three drive frequencies, an image is reconstructed. To establish the relation between frequency response and spatial position, a calibration scan with a dedicated voxel-sized reference sample has to be performed once for a given combination of scanner setup and tracer material. The ‘system function’ acquired in this calibration scan is necessary for solving the inverse reconstruction problem (Weizenecker et al. 2007).

The initial MPI scanner setup (Gleich and Weizenecker 2005) combined 1D FFP motion as described above with orthogonal mechanical FFP movement to achieve 2D spatial encoding. However, the mechanical spatial encoding scheme was far too slow to be useful for medical applications. A second drive field was introduced to overcome the speed limitations for two-dimensional imaging (Gleich et al. 2008). Real-time MPI with 250 frames per second was demonstrated in phantom experiments using a 2D Lissajous FFP trajectory. While these experiments required tracer concentrations which were of orders of magnitude higher than clinically applicable dosages, simulations (Weizenecker et al. 2007) indicated that imaging with physiologically tolerable tracer dosages could be feasible. Despite these theoretical findings, for in vivo imaging, agglomeration of the nano-particles due to contact with tissue could not be excluded. This would strongly degrade the MPI signal while leaving the MRI performance almost unchanged.

To realize the level of speed and sensitivity required for volumetric in vivo imaging, several innovations and improvements had to be introduced into the scanner concept previously used for dynamic 2D imaging.

Methods

Figure 1 schematically shows the basic setup of the 3D scanner. The scanner has an effective bore size of 32 mm. A pair of permanent magnets and a pair of coils produce the selection field gradient. The permanent magnets contribute 3 Tμ₀⁻¹ m⁻¹ and the coils 2.5 Tμ₀⁻¹ m⁻¹ to the magnetic field gradient, respectively. This gradient strength is achieved in the vertical direction in the yellow-framed images in figure 2. The scanner uses three sets of drive field coils to enable 3D imaging. The drive field \( H_D \) with an amplitude of 18 mTμ₀⁻¹ in the vertical direction is produced by the selection field coils. The drive fields in the two orthogonal directions are produced by dedicated coils which are driven at the same amplitude. Three drive field frequencies are chosen to move the FFP along a 3D Lissajous trajectory. The frequencies for the three directions are 2.5 MHz/99 ≈ 25.25 kHz, 2.5 MHz/96 ≈ 26.04 kHz and 2.5 MHz/102 ≈ 24.51 kHz, respectively. The Lissajous trajectory has a repetition time of 21.5 ms, corresponding to encoding 46.42 volumes per second, and covers a volume of about \( 20.4 \times 12 \times 16.8 \) mm³. The size of the gaps in the Lissajous pattern was chosen to match the desired resolution on the order of 1 mm. Two saddle-type receive coil pairs are aligned approximately perpendicular to the bore. In the axial direction, the solenoid drive field coil is also used for receiving the signal.

A new receive amplifier concept was implemented to reduce noise by a frequency-dependent factor between 5 and 100. In an ideal scanner, noise in the receive chain is only generated by current fluctuations in the patient, while in reality, coil noise and receive amplifier noise contribute to the noise level. MRI achieves patient-dominated noise, because the small signal bandwidth allows mitigation of the amplifier noise contribution by resonant matching.
Figure 2. Dynamic MPI images fused with static MRI images. Dynamic MPI images (left) and their fusion with static MRI images (acquisition time 23 min) in orthogonal views at selected points in time. The MPI video acquisition (21.5 ms per volume) started before injecting the tracer (Resovist) into the tail vein. The colored triangle in the overlay indicates the position of the orthogonal slices highlighted by the corresponding color frame. The position of the slices in the MRI volume is also given by the three numbers at the corners of the frames and is not always kept constant between the different images. The time axis on the right side describes the successive phases of the bolus passage. The spatial and temporal resolution enables resolution and identification of all heart chambers as well as parts of the vessel tree.

This strategy fails in MPI, since the receive signal is distributed over a wide frequency range. To provide the essential noise reduction, we designed a liquid cooled J-FET-based amplifier reaching an input noise voltage of 80 pV Hz$^{-1/2}$ (input capacity 1 nF) over the relevant frequency band from 50 kHz to 1 MHz. In addition, the noise voltage of the receiving coils...
alone is 50 pV Hz$^{-1/2}$ so the total noise is about 100 pV Hz$^{-1/2}$. In the current setup, the noise contribution of the mouse is negligible due to its small size and the associated low coil loading (Vlaardingerbroek and den Boer 2003).

Before the animal experiments, the system was calibrated by acquiring a system function. It was measured on a grid of $34 \times 20 \times 28$ with a voxel size of $(0.6 \text{ mm})^3$ using a small reference sample of undiluted $(500 \text{ mmol (Fe) l}^{-1})$ Resovist (Schering AG, Berlin). To a certain degree, the chosen voxel size is arbitrary; however, it should be smaller than the true resolution, which is determined by particle properties, selection field gradient strength and the level of regularization used in image reconstruction (Weizenecker et al 2007). In other words, in MPI, the voxel size is not equivalent to image resolution. The reference sample had cubic shape with the extensions exactly matching the voxel size of the grid. It was positioned and measured at all voxel positions of the grid. Positioning was performed using a robot (Flachbettanlage 1, Iselautomation KG, Eichenzell, Germany). The data acquisition time per grid point was 0.6 s. The total measurement time including robot motion and background measurement was about 6 h.

For reconstruction, the functional $\|G\tilde{C} - \tilde{U}\|^2 + \lambda \|C\|^2$ was minimized using a row relaxation method called algebraic reconstruction technique (ART) (Dax 1993, Kaczmarz 1937). Here, the matrix G represents the system function, $U$ is the measured mouse data, $C$ is the desired image, and $\lambda$ is a regularization parameter chosen to adjust the balance between SNR and resolution for best visual image impression. True image resolution depends on the regularization parameter and is usually lower than the voxel resolution. The iterative reconstruction approach does not require the inversion or factorization of the huge 3D system function matrix and furthermore allows for easy integration of reconstruction constraints into the iteration to account for a priori knowledge. This feature has been used to improve the image quality by the exclusion of unphysical negative tracer concentrations in the image.

The image resolution and SNR are not completely homogeneous over the entire field of view (FOV). The reason is the physical constraint of having a different selection field gradient strength in at least one direction. In our case, the gradient in the anterior–posterior (AP) direction (vertical direction in the yellow- and green-framed images in figure 2) had twice the strength of the orthogonal gradients. In addition, the speed of the FFP motion is lower at the edges of the FOV, thereby stimulating only a weaker particle response, which leads to a lower SNR and resolution in these regions, and a signal fade-out right at the rim.

The series of in vivo experiments comprised scans on 18 mice using different concentrations of Resovist (Lawaczek et al 1997). Ten of the experiments were conducted with dosages low enough for human usage, approximately ranging between the standard dosage of $8 \mu\text{mol(Fe) kg}^{-1}$ Resovist used in MRI scans, and a dosage of $45 \mu\text{mol(Fe) kg}^{-1}$, which is slightly above the safe dosage of $40 \mu\text{mol(Fe) kg}^{-1}$ for human applications (Schering 2004). The local license authority approved animal examinations. After a mouse (female NMRI outbred mice, Charles River Laboratories, Sulzfeld, Germany) was anaesthetized with 120 mg kg$^{-1}$ ketamine and 16 mg kg$^{-1}$ xylazine, an insuline syringe (BD Micro-Fine +, 0.5 ml) filled with $20 \mu l$ diluted Resovist was introduced to the tail vein and attached to the tail. Resovist was diluted in physiological saline solution. To achieve a dosage of $45 \mu\text{mol(Fe) kg}^{-1}$, a 10% dilution was prepared for a 22.4 g mouse. For a dosage of $10 \mu\text{mol(Fe) kg}^{-1}$, a 2.5% dilution for a 24.5 g mouse was used. The mouse was then placed in the supine position on a cylindrical animal support with an inner diameter of 29 mm so that the heart was within the FOV after insertion into the scanner bore. The raw data acquired after bolus injection were reconstructed to 1800 3D volumes.

To relate the MPI signal to the mouse anatomy, reference MR images of the sacrificed mice were acquired after the MPI scans for selected mice. The mice were carefully transferred
from the MPI system to the dedicated MRI animal support to facilitate later image fusion. The MR scanner was a commercial 3.0 T human whole-body scanner (Achieva 3.0 T, Philips, The Netherlands) with a mouse coil inset for high SNR signal reception. A standard T1-weighted turbo-spin-echo (TSE) sequence was applied to acquire sagittal multi-slice data. A FOV of $48 \times 80 \times 27\text{ mm}^3$ was covered with an in-plane resolution of 0.25 mm and a slice thickness of 0.50 mm. Total scan time amounted to 23 min. After interpolating the MPI data to the MRI resolution, image overlays were made by manual rigid-body registration using 3D translations according to different anatomical landmarks such as the vena cava and the heart chambers. In the overlay images, the MPI data are displayed using a color map with a color change from red to yellow to allow an easy differentiation from the grayscale MRI data and a high dynamic range.

**Results**

From the 18 exams, two representative results have been selected for presentation.

In figure 2, the dynamic MPI data are displayed and compared to the static MRI data obtained with a dosage of 45 $\mu$mol(Fe) kg$^{-1}$ Resovist. Due to the high temporal resolution, no triggering or gating was necessary to compensate for motion. In figure 2(A), the bolus enters the FOV via the vena cava. Due to the anisotropic gradient strength described above, the MPI resolution in the AP direction is better than in the orthogonal directions. Thus, in the left–right direction, the MPI signal is not completely confined to the vena cava visible in the MR image. In figure 2(B), the tracer just reaches the right atrium. It can be deduced that the vena cava crosses different sagittal slices to end up at the atrium. The right ventricle fills with tracer just after the right atrium. Figure 2(C) displays the tracer concentration three heartbeats later. The right ventricle is clearly visible from the MPI data and matches the MRI data. Moreover, the pulmonary arteries can be identified in the transversal slice of the MPI data. The intensity around these arteries increases over time (see figure 2(D)), which can be attributed to the filling of the pulmonary veins. The small vessels in the lung contribute to an average signal. After passing the lung cycle, the tracer reaches the left heart chambers. The left ventricle can be identified clearly in figure 2(E). In the transversal (green) and sagittal (yellow) slice of the MPI data, the left and right ventricles can be distinguished. Selected slices presented in figure 2 are also available online as a full video sequence showing the bolus passage (supplementary information) (stacks.iop.org/PMB/54/L1).

To exploit the high temporal resolution of MPI, concentration dynamics at selected voxels (vena cava, right and left atria, right and left ventricles) is presented in figure 3. The bolus passage through the vena cava and the four heart chambers is reproduced by the time-shifted concentration maxima at the different positions. This supports the mapping of anatomical features presented in figure 2. From the time shift between the right and left heart-chamber filling, the time for the lung passage can be estimated to be about 1.4 s. Furthermore, at the heart chamber positions, a modulation of the concentration can be observed. Due to the temporal onset, the modulation frequency and the opposite phase observed in the atria and the ventricles, we assume that this apparent concentration modulation results from the heart beat. The limited resolution leads to a partial volume effect creating an apparent concentration modulation, even if the real particle concentration within a heart chamber was constant. The heart rate of the mouse can be determined to about 240 beats per minute, which is low for a mouse, but can be expected for ketamine/xylazine anaesthesia (Janssen et al 2004). Additionally, the concentration dynamics in the vena cava shows the second and third passages of the bolus, as displayed in the inset graph in figure 3. The total time, which the tracer needs to pass the whole circulatory system, is about 5.1 s.
After injecting into the tail vein, the magnetic particles first arrive in the vena cava, then in the right atrium and the right ventricle. As expected, the contractions of the atrium and the ventricle are out of phase. Blood needs about 1.4 s to pass the pulmonary circulation and is then observed in the left atrium and the left ventricle. The contractions of the atrium and the ventricle are again out of phase, whereas the contractions of the left and right ventricles are in phase. From the periodicity of the contractions, a heart rate of 240 beats per minute is derived. The small crosses on the curve of the left ventricle illustrate the sampling points. Finally, a second pass and a third pass through the body with a respective delay of about 5.1 s produce the shallow concentration peaks as seen in the inset. The spatial distribution of the concentration at times (A)—(E) is displayed in figure 2.

Results of an experiment with a dosage of 10 \(\mu\)mol(Fe) kg\(^{-1}\) are presented in the supplementary videos 10–12 and in the supplementary figure 1 (stacks.iop.org/PMB/54/L1). All features discussed above can also be identified in these images, however with a higher artifact level than observed for the 4.5 fold dosage.

Discussion

The MPI results presented here do not indicate a drop in tracer performance in the in vivo situation. The data provide a spatial and temporal resolution sufficient for the identification of different structures in the beating mouse heart. For example, the left and right pulmonary arteries with a diameter of about 500 \(\mu\)m (Chesler et al 2004) can be observed albeit not fully resolved, being a structure which is considerably smaller than the smallest coronary arteries usually treated in humans. While with better contrast agents, high-resolution imaging with MPI is potentially feasible (Weizenecker et al 2007), it is difficult to assess the resolution achieved with the current agent in the in vivo situation. As described above, resolution also depends on the level of regularization in the reconstructed image. From the comparison of the vena cava cross section in the MR image and the MPI image, we estimate the achieved MPI resolution to be roughly 1.5 mm in the AP direction and 3 mm in the orthogonal directions. On the other hand, the vena cava is located close to the edge of the FOV, where, as described above, the resolution is reduced. At the center, we therefore expect a higher resolution of about 1 and 2 mm for the respective directions. A resolution of this order is also found in phantom experiments (Gleich et al 2008).
In the following, we try to assess the performance to be expected of a human whole-body MPI scanner.

Scaling the system for human applications increases the patient noise contribution, so that SNR estimations have to consider the coil, amplifier and patient noise. We estimate that with single-loop receive coils, due to the different scaling of noise contributions with size (Wang et al. 1995), amplifier noise would be dominant. With the demonstrated technology, the SNR in the human-size system would be at around 10% of the SNR shown here. However, other amplifier concepts (parametric amplifier, SQUID-based amplifier), cryogenic cooling of silicon J-FET amplifiers or modified tuning can lower the amplifier noise contribution to the level of the patient noise contribution. To compare the mouse scanner with a hypothetical improved human-size system, we have to compare the respective ratio between coil sensitivity and noise voltage at a given bandwidth. With the current system, noise voltage as stated above is about 100 pV Hz\(^{-1/2}\) while receive coil sensitivity at the isocenter is about 150 \(\mu\)T A\(^{-1}\) (24 loop coil split into two circular coils with a mean diameter of 18 mm and a coil separation of 36 mm). In a patient-noise limited human-size scanner, as described in a previous simulation study (Weizenecker et al. 2007), patient noise voltage is 1.8 pV Hz\(^{-1/2}\) (at 1 MHz) and coil sensitivities are 1.4 \(\mu\)T A\(^{-1}\) (single-loop rectangular receive coil (10 \(\times\) 10 cm) at 10 cm depth). If the same particle concentration is imaged at identical resolution using a comparable scanning sequence, the SNR scales proportional to this ratio, i.e., in the human-size system, the expected SNR would be 52% of the SNR found in the present system. Further room for improvement exists in the magnetic particles, encoding sequences and reconstruction algorithms, potentially summing up to a factor of more than 100 (Gleich and Weizenecker 2005; Weizenecker et al. 2008).

A selection field strength of 5.5 \(T\mu_0^{-1} m^{-1}\) can also be achieved over a large FOV; however, without expensive superconductors, only about 3 \(T\mu_0^{-1} m^{-1}\) might be feasible. Resolution with this selection field strength would probably be slightly too low for the direct assessment of the diameters of relevant human coronary arteries. However, using the ability to quantify particle concentration (and therefore indirectly, blood volume) and using the dynamic information, stenoses should be detectable. On the other hand, as described above, technical improvements still offer the potential of substantially higher resolution.

Regarding patient heating, the chosen combination of drive field amplitude and frequency may be feasible, since at the fourfold frequency, an amplitude of about 10 mT has been reported to be applicable to humans (Wust et al. 2006), corresponding to fourfold patient heating compared to our parameters. Heating scales with the square of the frequency and the square of the drive field amplitude (Vlaardingerbroek and den Boer 2003). In the cited publication (Wust et al. 2006), no peripheral nerve stimulation is reported; however, further research is required to find drive field frequency, amplitude and spatial distribution that minimize the risk of stimulation. Moreover, for coronary imaging, the drive fields may be applied for only a few seconds, allowing an increase in drive field frequency, improving the already excellent temporal resolution further. To cover the whole heart, an additional field similar to the drive field but at a lower frequency (<100 Hz) can be applied. This ‘focus field’ can move the volume covered by the drive fields to any volume of interest. This patching method has the additional advantage that the encoding speed of the sub-volumes is unchanged, which minimizes motion artifacts within each sub-volume. From these considerations, we infer that a human scanner can be realized without significant loss in speed and resolution.

Additional potential for improving MPI can result from optimized FFP trajectories, more efficient reconstruction approaches and improved tracer material. For the sake of technical simplicity, we used a Lissajous trajectory for the FFP motion. However, more sophisticated trajectories may be possible to improve the signal quality as discussed in Weizenecker et al.
Additionally, more a priori knowledge about the object can be used in the reconstruction to improve the image quality and speed, as it is already done in CT and MRI (Tsao et al. 2003, Mistretta et al. 2006, Li et al. 2004, Liang and Lauterbur 2000). The highest potential, however, can be found in the tracer material. As already shown elsewhere (Gleich and Weizenecker 2005), in Resovist, the fraction of the magnetic particles contributing to the MPI signal is only a few percent. Thus, the applied concentration might be lowered by at least one order of magnitude provided the adequate separation technique can be found. New approaches for particle synthesis may even improve tracer response determined by the slope of the tracer magnetization curve, allowing for lower selection field strengths and an increased spatial coverage, therefore resulting in a higher imaging speed.

To conclude, in this letter, we showed that magnetic particle imaging can image a beating mouse heart with high temporal and spatial resolution, using a commercially available MRI tracer material at clinically tolerable dosages. The results show that the new imaging modality MPI is capable of in vivo imaging and therefore has the potential to become a clinically adopted imaging modality.

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