Magnetic particle imaging for aerosol-based magnetic targeting

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Magnetic targeting is a strategy for improving the efficacy of therapeutic agents and minimizing the unwanted side effects by attaching the therapeutic agents to magnetic nanoparticles (MNPs) and concentrating them to the targeted region such as solid tumors and regions of infection using external magnetic fields. This study was undertaken to investigate the usefulness of magnetic particle imaging (MPI) for monitoring the effect of aerosol-based magnetic targeting by phantom experiments using a simple flow model and nebulized MNPs. Our results suggest that MPI is useful for monitoring the effect of aerosol-based magnetic targeting. © 2017 The Japan Society of Applied Physics

Magnetic nanoparticles (MNPs) have been used in various medical imaging fields such as magnetic resonance imaging (MRI) and magnetic particle imaging (MPI). MPI is an imaging method that was introduced in 2005.1) MPI allows the imaging of the distribution of MNPs with high sensitivity, high spatial resolution, and high imaging speed.2) In addition, MPI can visualize MNPs in a positive contrast with no signals from background tissues and can quantify the number of MNPs with excellent linearity.3) These advantages have been shown to be useful for various medical applications such as vascular imaging,4) stem cell tracking,5) cancer imaging,6) and magnetic hyperthermia.7)

Magnetic targeting has been developed for localizing drug carriers such as liposomes containing both MNPs and therapeutic agents in the targeted organ or tissue by applying external magnetic fields.8) The magnetic targeting of therapeutic agents results in the concentration of the agents at the targeted site, consequently reducing or eliminating systemic unwanted side effects.7) Recently, a new magnetic targeting strategy called “aerosol-based magnetic targeting” has been introduced for lung diseases.8) Aerosol-based magnetic targeting uses magnetic aerosol droplets comprising nebulized MNPs and therapeutic agents.8) The targeted delivery of magnetic aerosol droplets to the lung has various inherent advantages in that the drug dose can be easily adjusted by changing the drug concentration in the aerosol droplets without binding the drug to MNPs and that several drugs can be applied simultaneously using only one MNP type. The most important feature in the aerosol-based drug delivery to the lung is the direct application of the drug in the liquid phase to the disease lesion in the lung, which leads to a fast onset of pharmaceutical action and reduced systemic side effects.8)

An accurate knowledge of the spatial distribution and number of magnetic aerosol droplets is crucial for enhancing the effect of aerosol-based magnetic targeting and for its optimization. We previously investigated the application of MPI to pulmonary imaging using nebulized MNPs and attempted to quantify the mucociliary clearance in the lung using MPI.9) To the best of our knowledge, however, the usefulness of MPI for monitoring the effect of aerosol-based magnetic targeting has not been investigated yet. In this study, we investigated it using a simple flow phantom simulating aerosol-based magnetic targeting.

Figure 1 illustrates our flow phantom simulating aerosol-based magnetic targeting. As shown in Fig. 1, our phantom consists of a straight silicon tube (16 mm in outer diameter, 12 mm in inner diameter, and 50 mm in length), a compressor-type nebulizer with a suspension reservoir (Omron NE-C28), a flow meter (Kofloc RK1710), an inhaler (Shin-Ei Industries Minic S-II), and a neodymium magnet (Sangyo Supply). The MNPs in the reservoir were nebulized using the compressor-type nebulizer and pumped out from the inlet of the silicon tube to the outlet using the inhaler. In this study, we used 5-fold-diluted M300 (Fe3O4, iron concentration: 1.2 mol/L and particle size: 17.1 ± 4.9 nm)(Sigma Hi-Chemical) as the source of MNPs. A neodymium magnet (diameter: 10 mm, length: 30 mm, and magnetic flux density on the surface: 0.5 T) was placed near the center of the silicon tube to attract the MNPs. Furthermore, we placed a cylindrical urethane sponge (10 mm in width) inside the silicon tube to hold the MNPs accumulating at the targeted site. The urethane sponge also simulates the lung tissue. The flow rate was controlled using the flow meter placed between the outlet of the silicon tube and the inhaler.

To image the distribution of MNPs accumulating at the targeted site in the silicon tube using MPI, we took out the silicon tube after the phantom experiments and imaged it using our MPI scanner.10) In this study, we used Osaka MPI Scanner II, which is an extended version of our previous scanner.10) In this scanner, two opposing neodymium magnets were used for generating a field-free line (FFL). The gradient strengths of the magnetic fields perpendicular and
parallel to the FFL were 3.9 and 0.1 T/m, respectively. A gradiometer coil was used for receiving the third-harmonic signals generated by MNPs. The frequency and peak-to-peak amplitude of the drive magnetic field were taken as 400 Hz and 20 mT, respectively. After 36 projection data were acquired by translating and rotating a sample in the gradiometer coil automatically, transverse images were reconstructed using the maximum likelihood-expectation maximization (ML-EM) algorithm with 15 iterations.11) For construction using the maximum likelihood-expectation maximization (ML-EM) algorithm with 15 iterations,11) For co-registered X-ray CT images. As shown in Fig. 4, the pixel values increased with increasing flow rate.

Figure 5 shows the relationship between the flow rate and the average MPI value, in which both the duration of inhalation were taken as 4 mm and 15 min, respectively. When regression analysis was performed using the phenomenological Box–Lucas equation,13) there was an excellent correlation between them ($r = 0.988$). As shown in Fig. 5, the average MPI value increased but tended to saturate with increasing flow rate. In this study, we investigated the usefulness of MPI for monitoring the effect of aerosol-based magnetic targeting using a simple flow phantom (Fig. 1) and nebulized MNPs. As shown in Figs. 2–5, the changes in the MPI image and average MPI value depending on $d$ and flow rate were clearly observed. When we investigated the correlation between the iron concentration of MNPs ($x$ in mg/mL) and the average MPI value ($y$) using phantoms, there was an excellent linear correlation between them with a correlation coefficient greater than 0.999 and a regression equation of $y = 0.183x + 0.0535$ (plot not shown), indicating that the average as 15 min. As in Fig. 2, the MPI images were superimposed on the X-ray CT images. As shown in Fig. 4, the pixel values increased with increasing flow rate.

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The moving distance of the MNP during the flow rate (\(\Delta r\)) is given by
\[
\Delta r = v_m \times t_F = \frac{mL_F}{3\pi\eta d_h} \frac{\partial B}{\partial r} \frac{1}{v},
\]
indicating that \(\Delta r\) is inversely proportional to \(v\). Although the number of MNPs passing through the cross section of the silicon tube is proportional to the flow rate, the moving distance of the MNP to the magnet side (\(\Delta r\)) is inversely proportional to \(v\) or flow rate as given by Eq. (3). This appears to be the main reason why there was a tendency for the average MPI value to saturate with increasing flow rate (Fig. 5).

As previously described, when investigating the relationship between \(d\) and the average MPI value (Figs. 2 and 3), the nebulized MNPs were inhaled for 15 min at a flow rate of 1.5 L/min, implying that the total inhaled volume was 22.5 L. We adopted the above values for inhalation duration and flow rate in consideration of both the capacity of our inhaler and the sensitivity of our MPI scanner. It has been reported that the tidal volume per respiration in healthy adults is approximately 0.5 L.\(^{15}\) When the inspiratory duration is 1 s, the inspiratory flow rate becomes 30 L/min, which is much greater than our flow rate. When the respiratory frequency is assumed to be 15 min\(^{-1}\), the above total inhaled volume (22.5 L) corresponds to the tidal volume summed up for 3 min or 45 respirations. For the investigation of more realistic cases, it would be necessary to increase the flow rate and shorten the inhalation duration.

A limitation of this study is that the MPI value was obtained from a single slice of the MPI image. Thus, the analysis using a single slice of the MPI image limits the accurate evaluation of the spatial distribution of MNPs and the amount of iron in the entire targeted region. For a more detailed analysis, it will be necessary to acquire three-dimensional data, evaluate the three-dimensional distribution of MNPs, and quantify the amount of iron in the targeted region from these data.

In summary, the present study suggests that MPI is useful for monitoring the effect of aerosol-based magnetic targeting.

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