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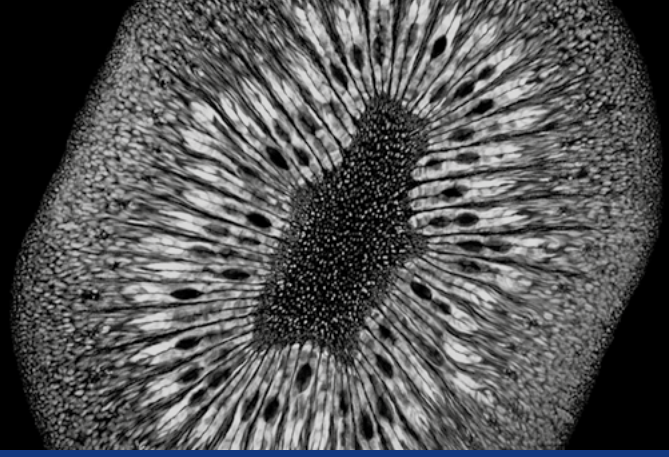

Innovative blood pool agent for MRI

Contrast-enhanced magnetic resonance angiography (MRA) using GadoSpin™ P

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Introduction

Blood pool agents are characterized by intravascular distribution and prolonged persistence in the blood allowing for the acquisition of diagnostic images with high spatial resolution. In comparison, conventional small-molecule imaging agents, which are generally used in the clinic, show rapid extravasation from the vascular space into the interstitium resulting in a relatively rapid decrease in vascular enhancement over time. Since the size of the imaging agent molecule is a main factor determining the distribution and elimination of the agent *in vivo*, macromolecules are excellent candidates as blood pool agents. Due to their larger size, macromolecular agents can potentially overcome the limitations of small molecules such as the rapid elimination from the blood pool, non-specific extravasation into surrounding tissue, and poor relaxation enhancement efficiency[1]. In addition, due to the enhanced permeation and retention (EPR) effect, macromolecular imaging agents can extravasate from fenestrated blood vessels into surrounding tissue of inflamed or tumorous areas. Thus, besides assisting contrast-enhanced magnetic resonance angiography (MRA), blood pool agents can also be used to target e.g., necrotic myocardium[2,3], or to detect various tumors[4,5]. In this study we tested the feasibility of GadoSpin™ P, a novel imaging agent composed of a high molecular weight gadolinium-containing polymer, to visualize the healthy mouse vessels *in vivo*.

Materials and methods

In order to obtain an indication of the signal-enhancing properties of GadoSpin™ P (Viscover™, *nanoPET Pharma* GmbH, Berlin, Germany) in comparison to those of the clinical small-molecule MRI agent, Magnevist® (Gd-DTPA, Bayer AG, Berlin, Germany), relaxivity measurements were performed prior to commencing the imaging experiments. The T_1- and T_2-relaxation times of aqueous solutions of either imaging agent were measured at varying Gd concentrations (2.5, 5, 10, 15 mM, n = 3 for each concentration) at 37 °C and 7 T using a PharmaScan® 70/20 scanner (Bruker BioSpin, Ettlingen, Germany), the device subsequently employed in the imaging experiments. Relaxivity values (r_1 and r_2) were calculated by estimation of the slope of the relaxation rate (1/T) as a function of concentration.

In vivo MRI was performed on isoflurane-anaesthetized healthy C57BL/6 mice (n = 12) before and after tail vein injection of either imaging agent (n = 6 per group) at a dose of 100 µmol Gd/kg body weight.

T_1-weighted images were acquired over a period of 40 min after contrast agent injection on the 7 T scanner described above using a T_1-weighted FLASH sequence (T_R = 15 ms, T_E = 3.5 ms, FA = 30 °, FOV = 30 mm, slice thickness 1 mm, 90 repetitions, 1 image/minute). To determine the time-dependent signal intensity in the blood, a region-of-interest (ROI) was placed in the inferior vena cava and its signal intensity was measured over time.

Results and discussion

The longitudinal and transverse relaxivities (r_1 and r_2) of GadoSpin P in water at 37 °C and 7 T were found to be 5.2 L mmol^{-1} s^{-1} and 11.3 L mmol^{-1} s^{-1}, respectively (Table 1). These values are considerably higher than those obtained for Gd-DTPA (r_1 = 3.7 L mmol^{-1} s^{-1}, r_2 = 7.4 L mmol^{-1} s^{-1}), the conventional small-molecule imaging agent in clinical use. This indicates that the innovative agent provides improved contrast at a particular magnetic field and Gd dose, and is most likely due to its longer rotational correlation time as a result of its polymeric structure[6].

So as to visualize the improved signal-enhancing properties of GadoSpin P *in vivo* as compared with Gd-DTPA, mice were injected with either contrast agent and imaged over a period of 40 min (Fig. 1). Immediately after administration of GadoSpin P, the signal intensities in the inferior vena cava and neighboring structures (including the kidneys) rapidly increased and were seen to persist over the entire imaging period. In comparison, while the signals in the blood increased after injection of Gd-DTPA, the signal intensities were much lower than those observed with GadoSpin P. Furthermore, the signal intensities observed with Gd-DTPA decreased rapidly with time, an effect that results from the agent's rapid extravasation and fast renal clearance.

In order to determine the blood half-life of GadoSpin P, the contrast-induced signal enhancement in the blood was measured over time (Fig. 2). From the plot, it is clear that the agent remains in the vascular system for a prolonged period. Due to the agent's long blood circulation time and complex pharmacokinetics, a standard mono- or bi-exponential fit could not be applied. Therefore, the blood half-life was estimated graphically and was found to be approx. 2 h. This long intravascular half-life is roughly 20 times higher than that of Gd-DTPA, which was found to be approx. 6 min, as determined from the mono-exponential fit of the time curve. GadoSpin P was found to be excreted mainly via glomerular filtration and was completely eliminated from the body after 24 h.

	Relaxivity (37 °C, 7 T, in water)	
	r_1 [L mmol^{-1} s^{-1}]	r_2 [L mmol^{-1} s^{-1}]
GadoSpin P	5.2	11.3
Gd-DTPA	3.7	7.4

Table 1: Longitudinal and transverse relaxivities (r_1 and r_2) of GadoSpin P and Gd-DTPA in water at 37 °C and 7 T.

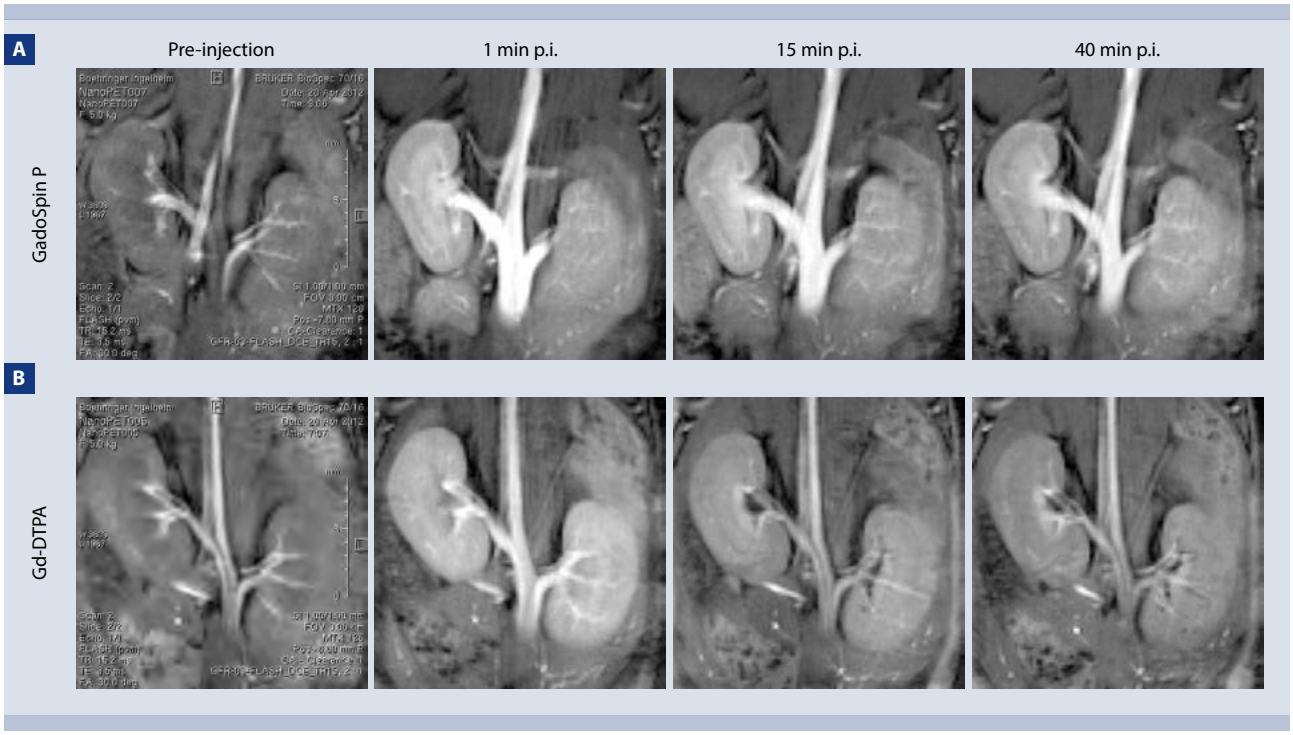

Figure 1: Coronal MR images (T_1-weighted) of the mouse kidney and adjacent blood vessels before and at various time points after intravenous injection of the imaging agent at a dose of 100 µmol Gd/kg body weight.
Application of **A.** GadoSpin P and **B.** Gd-DTPA show that GadoSpin P provides significantly higher signals in healthy vessels, which persist for a longer period of time.

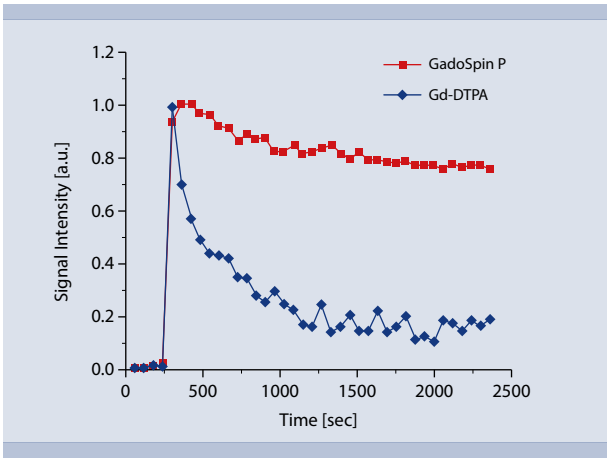

Figure 2: Time course of the T_1 signal intensity in the blood measured over a period of 40 min after intravenous injection of imaging agent at a dose of 100 µmol Gd/kg body weight.
The time-dependent signal intensities obtained after administration of GadoSpin P show that, compared to conventional Gd-DTPA, the innovative imaging agent remains in the vascular system for a prolonged period of time.

Conclusion

In this work we performed *in vivo* contrast-enhanced magnetic resonance angiography (MRA) in the healthy mouse using GadoSpin P. The study shows that GadoSpin P acts as an intravascular MR imaging agent having high contrast efficiency as well as optimal biocompatibility and clearance properties. The agent enables higher resolution images through improved contrast and a pronounced steady state period, which serves to increase the temporal imaging window, thereby allowing more accurate disease diagnosis. Its long blood half-life and renal clearance render GadoSpin P useful as an imaging agent for blood pool imaging as well as for studies of renal structure and function.

Viscover™ Product	Order No.
GadoSpin™ M, 1 x 5 injections	130-095-134
GadoSpin™ M, 5 x 5 injections	130-095-135
GadoSpin™ P, 1 x 5 injections	130-095-136
GadoSpin™ P, 5 x 5 injections	130-095-137
GadoSpin™ F, 1 x 5 injections	130-095-162
GadoSpin™ F, 5 x 5 injections	130-095-163
GadoSpin™ D, 1 x 5 injections	130-095-164
GadoSpin™ D, 5 x 5 injections	130-095-165

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