

In vivo visualization of pancreatic islets in the mouse

D. Z. Balla¹, S. Gottschalk¹, G. Shajan¹, S. Ueberberg², S. Schneider², R. Pohmann¹, and J. Engelmann¹

¹High-Field MR Center, Max Planck Institute for biological cybernetics, Tübingen, Germany, ²Universitätsklinikum Bergmannsheil, Ruhr-Universität Bochum, Bochum, Germany

Introduction

Beta-cells inside the pancreatic islets of Langerhans are the only source of the hormone insulin. Visualization of pancreatic islets with MRI in the mouse has many potential applications in preclinical diabetes research, because the amount of beta-cells decreases with the onset of the disease. Islets of Langerhans were imaged with a beta-cell specific MRI contrast agent in the excised murine pancreas [1]. For the in vivo detection, methodical optimization both on the acquisition and on the reconstruction side is necessary. First in vivo images from the mouse abdomen, which show similar local contrast in the pancreas as the one obtained in ex vivo data, are presented here.

Methods

The beta cell specific antibody-fragment SCA1 B1 [2] was coupled to superparamagnetic cobalt nanoparticles (NP) and was injected i.v. as suspension in C57BL/6J-mice with a dosage of 50µg SCA1 B1 (corresponding to 1500µg NP) in 150µl PBS. Experiments were performed on 16.4T. Eight to twelve hours ex vivo scans were conducted with fast 3D gradient echo sequences and achieved an isotropic resolution of 50µm. The same resolution can not be reproduced in vivo with the required signal-to-noise ratio (SNR). 3D spatial encoding in combination with respiration gated or navigator based sequences for high resolution takes longer than acceptable under in vivo conditions, and at lower resolutions the small ($\varnothing < 100\mu\text{m}$) islets are hardly discernible because of partial volume effects. Thus, very high resolution in- and through-plane 2D sequences are needed. Results acquired with the following two approaches are presented: 1. Susceptibility weighted imaging (SWI) using respiration triggered 2D-FLASH acquisition followed by iterative multiplication of the magnitude image with a phase dependent weighting mask [3]; 2. Fast navigator-based 2D double-slice IntraGate-FLASH with multiple repetitions for sampling and subsequent demerger of motion effects.

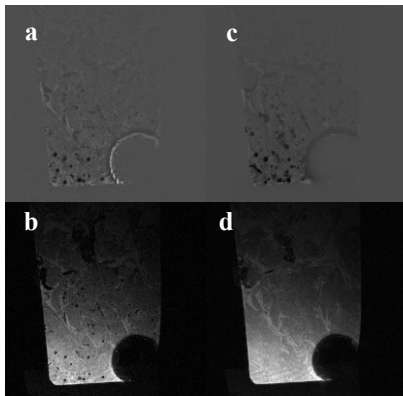


Figure 2: Ex vivo images of an excised pancreas acquired with a surface coil (50µm isotropic). Original single slice images: (a) SWI. (b) Magnitude. (c) Minimum intensity projection SWI through 6 slices. (d) Average magnitude over 6 slices.

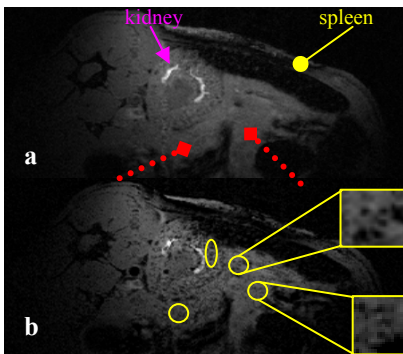


Figure 3: Triggered 2D-FLASH images of a mouse abdomen acquired with a surface coil. TR~600ms (respiration period), TE=1.9ms, 100x100x300µm³, NA=2. (a) Magnitude image. (b) SWI. Pancreatic tissue is marked (red arrows); contrast enhanced regions are highlighted and two zoom-ins are presented as insets.

References: [1] Gottschalk S. et al., (2010) Proc. ISMRM; [2] Ueberberg S. et al., (2009) Diabetes 58:2324; [3] Haacke EM et al., (2004) MRM 52:612

Results

Ex vivo images show negative punctual contrast in the pancreas (verified by immunohistochemistry [1]) and kidney, and global signal cancellation in liver and spleen (Fig.1). After injection of similar NP without SCA1 B1 no effect was detected in the pancreas (data not shown). The susceptibility contrast seen in Fig.1a was reproducible in vivo with both triggered and navigated 2D gradient echo sequences with in-plane resolution $>75\mu\text{m}$ and a slice thickness $>300\mu\text{m}$ for liver, spleen and kidney (data not shown). However, the fine structural contrast created by the particles accumulated in pancreatic islets could not be observed. Figure 2 presents ex vivo susceptibility weighted- and magnitude images of an excised pancreas. Images in Fig.2a-b have the original through-plane resolution of 50µm. Islets are clearly visible. The SWI in Fig.2c is the minimum intensity projections of 6 planes, whereas the magnitude image in Fig.2d is the average of those 6 planes, simulating a 300µm slice. Particle contrast dramatically decreases with through-plane resolution. In Fig.3 2D-FLASH in vivo images acquired with 100x100x300µm³ resolution are presented (same mouse whose pancreas is shown in Fig.2). In the original magnitude image (Fig.3a) no negative contrast in the kidney or the pancreas can be seen, similar to the averaged magnitude image in Fig.2d. In the SWI (Fig.3b) a regional intensity decrease both in the kidney and the pancreas can be observed. However, the expected punctual contrast seems to be blurred, presumably due to the through-plane partial volume effect, and a clear localization of the islets is not possible. In control animals this regional contrast change was not observed (data not shown). Figure 4 shows double-slice IntraGate-FLASH images with 66x66x100µm³ resolution (same mouse as in Fig.1a). This exceptional in vivo resolution in the abdomen could be achieved with high SNR in 11 minutes, because no triggering was needed and a short repetition time could be set. The contrast is very similar to the ex vivo contrast shown in Fig.1 and pancreatic islets can be detected in both slices. Longer repetition times allow for the acquisition of more slices at the cost of measurement time. However, the double-slice version can be used with exactly the same repetition time as the ex vivo 3D-scan.

Conclusion

In vivo visualization of pancreatic islets in the mouse is feasible with the help of targeted contrast agents and high resolution gradient echo imaging at 16.4T. Two approaches were described. Triggered sequences suffer from their intrinsic minimal repetition time, which is usually one respiration cycle and prevents them from being as signal-efficient as navigator-based sequences. Using the usually ignored phase information of the signal, the images can be processed to give better susceptibility-contrast. However, the limited through-plane resolution blurs multiple local signal dropouts and detection of single islets is difficult. Nevertheless, triggered high resolution sequences can be sensitized to the regional amount of pancreatic islets. As second approach, a double-slice IntraGate-FLASH sequence was used in vivo to produce ultra high resolution images and to detect the distribution of paramagnetic particles in the pancreas. Single islets of Langerhans in the mouse were visualized for the first time in vivo with MRI after i.v. injection of targeted contrast agents.

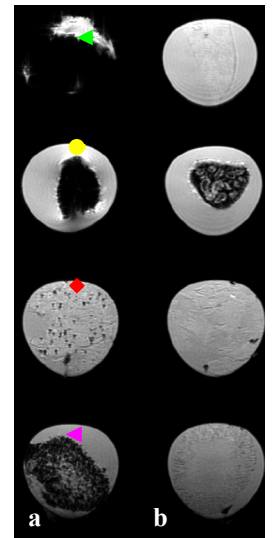


Figure 1: Ex vivo images of liver, spleen, pancreas and kidney (from top). (a) Marked. (b) Control. TR=15, TE=4.25ms. Green = liver; yellow = spleen; red = pancreas; violet = kidney.

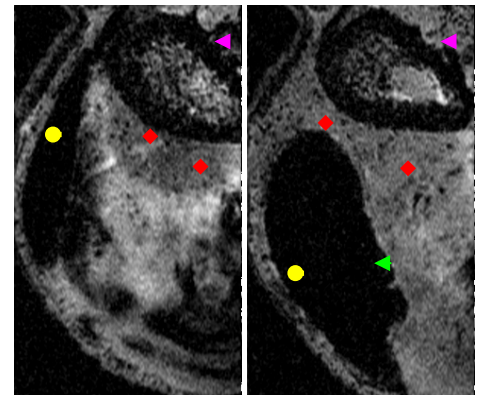


Figure 4: Double-slice IntraGate-FLASH images of the mouse abdomen (volume coil). TR=15ms, TE=2.75ms, NR=250, 66x66x100µm³, slice gap 2mm, FOV=10x23mm, horizontal readout, ACQ=11min.