In Vivo Identification of Iron-Marked Cells in the Heart by Gadolinium-Enhanced MRI in a Single Breath-hold

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Introduction

Cellular imaging is an emerging field that uses high-resolution magnetic resonance imaging (MRI) along with super paramagnetic iron oxide (SPIO) based contrast agents compartmentalized in cells to visualize and identify small numbers of cells. The paramagnetic nature of the SPIOs in labelled cells induces susceptibility inhomogeneities, which result signal attenuation in the surrounding tissue. The in vivo identification of the signal attenuation due to the SPIOs with the established gradient or spin echo sequences is difficult, because other mechanisms contribute also to signal attenuation like the surface between tissue and air. Therefore, a new approach for distinct identification of cells in vivo is necessary. A promising method is the "White marker" technique based on an unbalanced Flash-Sequence [1], which visualizes the susceptibilities induced by iron with positive contrast. The difficulty of this approach is the long acquisition time required to obtain an acceptable contrast-to-noise ratio (CNR) of the labelled cells. On this account, and due to the motion of the heart and the attended short acquisition time, a verification of the existence of labelled cells with positive contrast-methods has not been feasible in the heart until recently.
The aim of this study was to visualize SPIO-labelled cells in the myocardium during a single breath-hold using positive image contrast.

Material and Methods

MR Imaging: The MRI measurements were performed on a 1.5 T Magnetom Vision (Siemens Medical Solutions, Erlangen, Germany) whole-body MR scanner with a custom-built whole body gradient insert capable of switching 50 mT/m gradients within 300 µs. However, not the available peak gradient power was used in this study. Signal reception was performed with a four-element phased-array coil; RF transmission was done using the built-in body resonator.
The "positive contrast" –imaging sequence was an unbalanced saturation recovery TFlash-sequence with a partially rephased slice-selection gradient (57%). The field of view was 300x300mm with 1.17 mm^2 pixel size, slice thickness was 8 mm, TI/TR/TE = 260 ms/1966 ms/3.4 ms, the flip angle was 20°. Two acquisitions during the same breath-hold were averaged. The additionally administered contrast agent was 14 ml/kg of Gd-DTPA (Magnevist, Schering, Germany).
For comparison a "negative contrast"- imaging sequence with attenuation of the surrounding of the labelled cells was used. For this purpose a 3-segmented two-dimensional FLASH pulse sequence was used (field of view, 380x380mm, image resolution, 1.48 mm^2, slice thickness 5 mm, TR/TE = 30 ms/4.8 ms, and flip angle 30°).
Cell loading: Peripheral blood progenitor cells derived with a Ficoll-gradient were incubated with super paramagnetic iron-oxide particles loaded micro spheres (0.9 µm) obtained from Bangs Laboratories (Fischers, IN). The particles are composed of a divinyl benzene matrix and contain 63.4% magnetite iron oxide [2].
Tissue Preparation: Two ml of a SPIO labelled cell suspension (concentration = 1.96*10^6 cells/ ml) were injected in 0.2ml portions in the myocardium of the left ventricle of a pig in vivo. After 4 weeks the heart was examined by magnetic resonance imaging. During the measurement the pig was narcotized and artificially respirated. The experiments were approved by the local ethic committee.

Results

In Fig. 1 the "negative contrast"- image an accumulation of labelled cells in the myocardium is shown in the long axis view of the heart. The two arrows point at the attenuation of the myocardial signal induced by the SPIOs. In the same slice Fig. 2 shows at the same positions bright signals caused by the susceptibilities induced by the SPIOs whereas the remaining myocardial signal is suppressed. This image was acquired 25 minutes after the injection of the contrast agent. In Fig. 3, measured 35 minutes after injection time, the positive signals of the SPIOs are decreased, because the contrast agent was almost washed out of the myocardium. This demonstrates that the use of the "positive contrast"-sequence alone is not sufficient to image the conglomeration of the SPIOs, but that the distinct visualization also requires the administration of additional contrast agent, which accumulates in the myocardium.

Discussion

In this study it was demonstrated for the first time that the definitive in vivo identification of SPIO-loaded cells with the introduced "positive contrast" technique in the myocardium within a single breath-hold is possible. The "positive contrast" of the cell conglomeration also depends on the given concentration of contrast agent and the myocardial accumulation time of it for a given number of labelled cells.

References

[1] Seppenwoolde *et al*, MRM 50:784-790 (2003); **[2]** Hinds *et al*, Blood Vol.102, Nr.3:867-872 (2003)

Ackknowledgement

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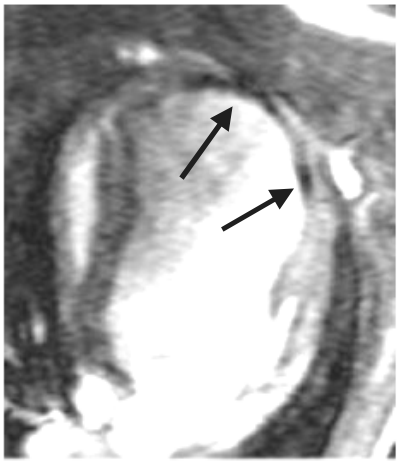

Fig. 1: „Negative contrast"-depiction of iron labelled cells without contrast agent in the long axis view of the heart.

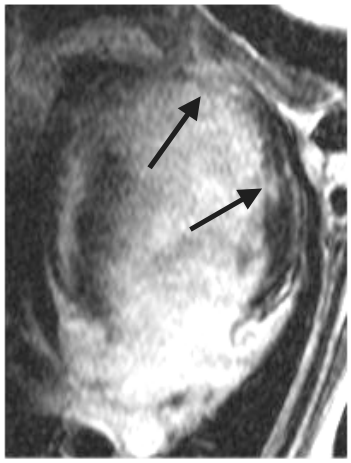

Fig. 2: „Positive contrast"-depiction at the same position with 14 ml/kg Magnevist, 25 min after injection of contrast agent.

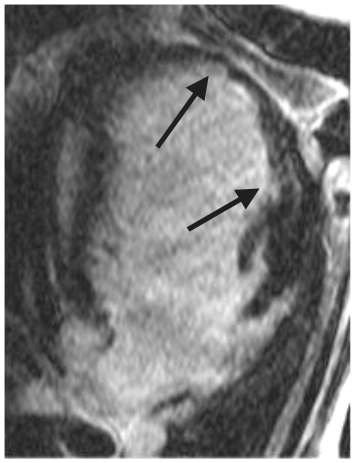

Fig. 3: „Positive contrast"-depiction at the same position with 14 ml/kg Magnevist, 35 min after injection of contrast agent.