A Dose Dependent Inflammatory Cell Tracking by Micrometer-Sized Iron Oxide Particles-Enhanced MRI in Murine Myocardial Infarction Model

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INTRODUCTION

Inflammation plays a pivotal role in the cardiac remodeling process following myocardial infarction (MI)[1]. Recently, it has been shown that inflammatory cells such as macrophages can be labeled with micrometer-sized iron oxide particles (MPIO) via systemic injection[2]. Upon surgically induced MI, the inflammatory cells can be activated and mobilized to the MI site. Signal attenuation caused by labeled cells around the MI site has been observed in T_2^*-weighted MR images. However, the MPIO dose warrants further optimization in order to acquire adequate signal attenuation while minimizing the dose. The purpose of this study is to investigate the relationship between the injected MPIO dose and the signal attenuation caused by labeled cell infiltration around the MI sites.

METHODS

C57Bl/6 mice (n=36, 6-11 weeks) were divided into three groups. The three dose groups were: high dose group (14.5 μg Fe/g body weight, n=11); low group (3.6 μg Fe/g body weight, n=16); and a control group,(no MPIO injection, n=9). The animals underwent MI via permanent ligation of left anterior descending coronary artery 7 days post-MPIO injection[2]. T_2*-weighted MR images were acquired at baseline, 3 days (D3), 7 days (D7) and 14 days (D14) post-MI on a 7-T, 21-cm horizontal Bruker BioSpec MR system using an ECG-gated gradient echo sequence with flow compensation (GEFC). The parameters were: TE/TR=4/120 ms; Field of view=30 mm; Matrix=256x256; Flip angle=30°; Slice thickness=1mm; Number of averages=8. Animals were sacrificed for histology after the terminal MRI session. MR images were processed with an in-house imaging analysis program written in MATLAB. Briefly, the signal intensity in each image was normalized to a range of 0 to 1. The left ventricular wall (LVW) was delineated manually, and the MI and two adjacent regions were identified automatically by curve fitting of the LVW thickness. Two-way ANOVA was used to compare the normalized signal intensity at the MI and two adjacent regions between any two of the three groups.

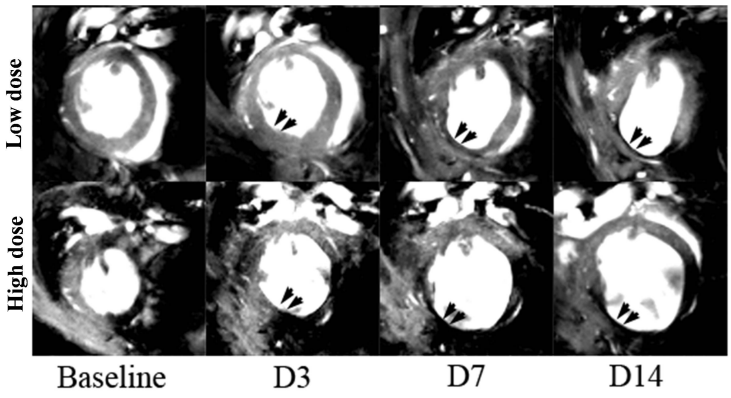

Figure 1. T_2^*-weighted temporal short-axis cardiac MR images. More signal attenuation was observed around MI sites for the high dose at each time point.

RESULTS

Signal attenuation was detected around the MI site due to the accumulation of MPIO-labeled inflammatory cells at both the high and low dose levels (Figure 1). The existence of MPIO-labeled macrophages was confirmed by histology. The signal intensity became further attenuated as cardiac remodeling progressed (Figure 1 and Figure 2). This indicated MPIO-labeled inflammatory cells continued to infiltrate into the infarcted heart. At the low dose level, the signal attenuation around the MI sites was not significant at D3 and D7 ($P>0.05$ for low dose versus control group at D3 and D7). However, significant signal attenuation around the MI site occurred at D14 ($P<0.01$ for low dose versus control group). At the high dose level, signal attenuation around MI sites was significant at all time points ($P<0.01$ for high dose versus control group at D3, D7 and D14). Furthermore, the T_2*-weighted MRI was able to differentiate the additional signal attenuation caused by increased labeled-cell infiltration.

CONCLUSIONS

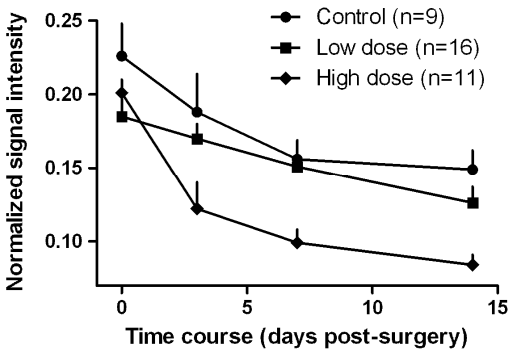

Figure 2. Dose dependent temporal plot of normalized signal intensity at MI sites.

MPIO-labeled inflammatory cell infiltration to MI sites can be monitored by T_2*-weighted MRI method in the murine model. This method could differentiate signal attenuation at various concentration levels. Since the post-MI inflammatory cell infiltration takes place continuously over 14 days post-MI, the signal intensity around MI sites was also increasingly attenuated with time. Although a dose level as low as 3.6 μg Fe/g body weight was enough for MR tracking of inflammatory cells at 14 days post-MI, a higher dose is required to ensure observable and significant signal attenuation at earlier time points such as 3 and 7 days post-MI. More experiments at other dose levels are necessary and ongoing in order to delineate the relationship between dose injected and signal intensity around the MI sites and to conclude the optimal dose.

REFERENCES

(1) Fujiwara N, Kobayashi K. Macrophages in inflammation. *Curr Drug Targets Inflamm Allergy.* 2005;4(3):281-6. (**2)** Yang Y, Yang Y, Yanasak N, Hu TC. *Magn Reson Med.* 2009; in press.