Detection of Focal Inflammation on Myocardial Disorder Using T2 Contrast Agent-based MRI: Comparison to Late-enhanced MRI with T1 contrast agent

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Introduction: Late enhanced-cardiac MRI using T1 contrast agent is known as the current standard of myocardial inflammation diagnosis. However, the poor sensitivity of late enhanced-cardiac MRI has hindered the reaching of a consensus on the clinical practice guidelines for its evaluation and treatment[1]. In this study, we investigated whether T2 contrast agent-combined CMR (cardiac magnetic resonance) imaging would be feasible and effective for the detection of the inflammation in a rat model of experimental autoimmune myocarditis (EAM) in comparison between T2 and T1 contrast agents, and whether T2 contrast agent-combined CMR imaging could give a guidance where the biopsy samples should be collected.

Materials and Methods: Myocardial inflammation was induced according to the reported induction method of experimental autoimmune myocarditis (EAM)[2] in four 7-week-old male Lewis rats. We used home-made magnetic nanoparticles (MNPs) T2 contrast agent that enable the detection of both their fluorescence and magnetic properties in cells and tissues[3] and Gd-DTPA (Magnevist®). We performed T2*- and T1-weighted MRI in EAM (n=4) rats before injection of contrast agents, then injected Gd-DTPA (0.2 ml/kg). 40 min after the Gd-DTPA injection, we acquired contrast-enhanced T1-weighted (Gd-enhanced) MR images. After the MR imaging, a bolus of MNPs was injected via tail vein (10 mg Fe/kg), and T2*-weighted (MNP-enhanced)MR image was obtained 24 hr after the injection. MRI measurement was performed using a 4.7 T MRI system (BioSpec 47/40; Bruker, Germany) with dual ECG and respiratory gating (SA Instruments, Stony Brook, NY, USA). T1-weighted MR images were obtained with a black-blood fast low-angle shot (FLASH) cine sequence (TE/TR = 2.8/8 ms) in the center, upper and lower side of the heart in axial direction. A gradient-echo (FLASH) sequence (TE/TR = 6/130 ms) was used for T2*-weighted imaging. After serial *in vivo* MR imaging, all hearts were extracted and performed with immunehistochemistry (IHC) staining and fluorescence microscopy imaging.

Results and Discussion: Thickened ventricular walls and pericardial and/or pleural effusion in some instances were noted in the EAM rats. Gd- and MNP-induced contrast patterns in the MR images were not uniformly homogeneous in the myocardium, especially in moderately inflamed hearts. There is small difference in the contrast patterns of Gd- and MNP-enhanced MR images, which could be elucidated from the dominated origins between edema and inflammatory cells, respectively. Some dark spots by negative contrast in MNP-induced MR images were obtained, while there was no significant enhancement in those spots of Gd-enhanced MR images. We obtained H&E- and IHC-stained images from the adjacent sections of same heart, which were compared with T1- and T2*-weighted MR images. The regions with infiltrated monocytes in the IHC-stained and H&E stain images are in good correlation with the positive and negative contrast areas by Gd-DTPA and MNP accumulation in MR images, respectively. These results support the potential of MNP-combined CMR as a valuable tool in the research and clinical applications. Furthermore, we expect that the MNP-contrasted CMR imaging could give us a guide where to take biopsy samples from the heart suspecting myocarditis, which will reduce making an error in diagnosis of human myocarditis.

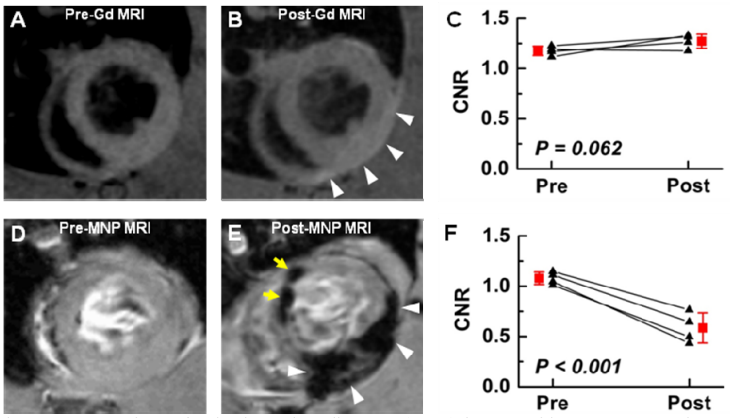

Figure 1. Comparison of Gd-enhanced cardiac MR (CMR) images with MNP-contrasted CMR images. Left wall became thick because of inflammation (A). The contrasted regions in Gd-induced MR image (arrowheads in B) are clearly shown in well colocalization with the area in MNP-induced MR image (arrowheads in E). Notice negative contrasted regions only in MNP-induced MR image (yellow arrow in E). The change of contrast-to-noise ratio (CNR) in the colocalized regions of pre- and post- MR images was dominant in MNP-induced MR images (P <0.001 vs P = 0.062).

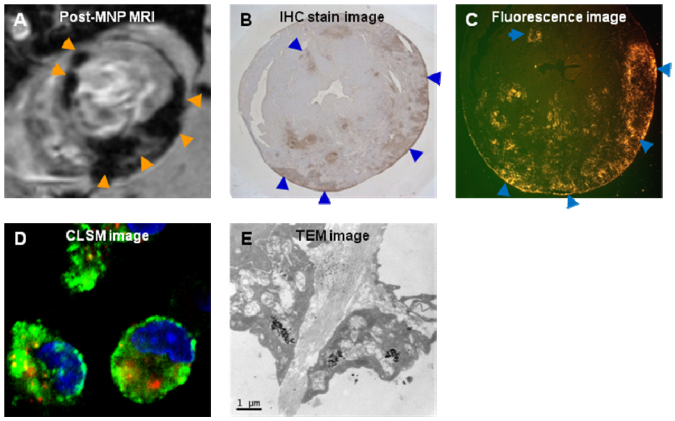

Figure 2. MNP-contrasted MR (A), IHC (B), and fluorescence (C) images are compared in almost same axial slice of EAM heart. Confocal laser scanning microscopy (CLSM; D) and TEM (E) images obtained from EAM myocardium are shown. Bright spots in MNP-contrasted MR image is well colocalized with the macrophage infiltrations in IHC-image and bright spots in fluorescence image. A merged CLSM image (D) is shown. In the CLSM image, a large number of monocytes labeled with MNPs in EAM were observed with red for RITC (MNP), green for Alexa Fluor488 (macrophage), and blue for DAPI (muclei). Furthermore, the accumulation of MNPs in lysosome of the monocytes was observed from the TEM image (E).

References

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