Visualization of Myocardial Inflammation in Experimental Autoimmune Myocarditis Rats detected by MR Imaging with a Magnetofluorescent Nanoparticles

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Introduction: Clinically, myocarditis is a major cause of sudden death in young adults, and leads to dilated cardiomyopathy in 9% of the cases in a large prospective series. Despite these significant consequences, the poor sensitivity and specificity of traditional diagnostic modalities have hindered the reaching of a consensus on the clinical practice guidelines for its evaluation and treatment.[1] In this study, we investigated whether MNP (magnetic nanoparticle)-contrasted CMR (cardiac magnetic resonance imaging) would be feasible and effective for the detecting the inflammation in a rat model of experimental autoimmune myocarditis (EAM), and whether MNP-contrasted CMR could give a guidance where the biopsy samples should be collected.

Materials and Methods: EAM was induced in forty one 7-week-old male Lewis rats.[2] In this study, we used bifunctional MNPs that enable the detection of both their fluorescence and magnetic properties in cells and tissues.[3] We performed MRI in EAM (n=5) and control rats without myocarditis (n=3) and compared the MR images obtained before and 24 hr after the intravenous injection of MNPs (12 mg Fe/kg) in order to determine whether the MNPs could provide MRI contrast in the inflamed myocardium. MRI 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). MNPs were intravenously administered (12mg Fe/kg), then we obtained MR images with a gradient-echo (FLASH) sequence (TE/TR = 6/150 ms). Serial CMR was conducted prior and 24 hr after the MNPs injection. We defined regions of interest (ROIs) for numerical analysis; ROIs of myocardium and pectoral muscle from 3 slices in the center of the hearts. From the selected ROIs, the mean SNR values were measured in the myocardium and the pectoral muscle, and they then were compared in control and EAM rats. After *in vivo* MR imaging, all hearts were stained with hematoxylin and eosin (H&E). The hearts were treated with mouse anti-rat macrophage monoclonal antibody clone ED-1.

Results: On the MR images before and 24 hr after the MNPs injection, there was little SNR change in the pectoral muscle in both the control and EAM rats. In contrast, in the myocardium, there was dramatic change (~75%) in the EAM rats, while it was decreased by ~13% in the control rats (Figure 1). These results show that the negative contrast in MR images may be attributable to the MNPs phagocytized by the monocytes in the inflamed myocardium, which was confirmed by CLSM images from the extracted heart tissue samples.[4] We sampled some cases between medium and peak inflammation phases, and categorized them as two groups depending on the MR contrast pattern whether they were contrasted homogeneously or heterogeneously in myocardium of the MR images at 24 hr post-injection. MRI examples from the two groups are shown in the Figure 2. We obtained H&E and IHC staining images from the same hearts, which are compared with MR images. From the H&E and IHC staining images, the regions with infiltrated monocytes are in good correlation with the negative contrast areas in MR images. In some cases, epicardial band-like MR contrasted hearts were also observed (bottom raw in the Figure 2), which may guide us where biopsy sampling should be done.

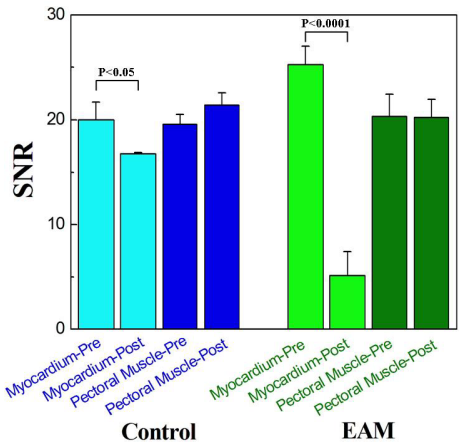

Figure 1. Shown are the measured SNRs in the myocardium and pectoral muscle of MR images before and after the injection of MNPs. There is a big SNR change in myocardium after the injection of MNPs in EAM rats.

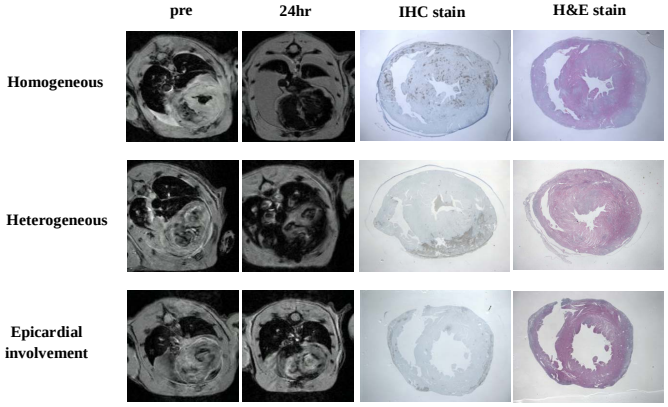

Figure 2. MNP-contrasted CMR images obtained at pre- and post-injection of the MNPs are shown, depending on the contrast pattern (1st and 2nd columns), and compared with the H&E and IHC staining images.

Conclusion: We demonstrated that the noninvasive imaging of myocardial inflammation is feasible in autoimmune myocarditis rats by using the MNP-contrasted CMR. This CMR approach combined with MNPs provides the feasibility and efficiency to image noninvasively and track myocardial inflammation in EAM rats. 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 could guide where we biopsy from the heart suspecting myocarditis, which will reduce making an error in diagnosis of human myocarditis.

References

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