Non-invasive analysis of the degree of inflammatory areas by in vivo time course MRI using long circulating nanoparticles in myocardial inflammation rat model

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Purpose: It is well-known that MNPs can help us where inflammatory areas are located using in vivo 24 h post-MNP MR imaging because of phagocytosis of macrophages infiltrated in the inflammatory sites. But, we can't know whether inflammation is severe or weak using 24 h post-MNP MRI. Even using the EGE and LEG methods, they have same problems. It is known that the brightened SI values reflect the living cell contents in cardiac MEMRI. Nevertheless, it can't exactly compare the immune cells in the inflammatory sites with normal myocardium. In our study, we investigated whether time course MNP-enhanced MRI could distinguish between the severe inflammatory sites, weak inflammatory sites, and normal tissues within 12 h after injection of MNPs having long blood-circulation time using myocardial inflammation induced rat models.

Methods: The MNPs were synthesized by co-precipitation method. These particles were coated with SiO_2 for increasing the biocompatibility and stability, and conjugated with PEG for extending the blood-half life time than other similar sized nanoparticles. Its blood half-life time is about 2.4 h in rats. The 5.0 mg Fe/kg of MNPs were injected via tail vein into experimentally induced myocarditis rats. During 24 h, we consecutively performed *in vivo* cardiac MR imaging and then extracted the hearts for histological study. We separated the myocardial tissues into normal myocardial tissues, severe inflammatory areas and weak inflammatory sites in the MR images. The severe and inflammatory sites were divided comparing with the macrophage IHC staining images. From these 3 sites, we acquired the contrast to noise ratio (CNR) values in each time point. In addition, we performed the time-series MNP-enhanced in vivo cardiac MR imaging in the normal rats. The CNR values were acquired in the myocardial tissues, too.

Results and Discussion: In the myocardial inflammation rat models, the CNR values measured on the normal myocardium are rapidly decreased to the minimum values within 30 minutes, then repaired to the pre-MNP injection values during 24 h. Same CNR change patterns is shown on the myocardium in the normal rats. However, in the inflammatory areas, the CNR values decay to the minimum values more slowly than in the normal myocardium. Its difference could be explained with blood vessels. The velocity of CNR changes within 2 h reflects the damage of blood vessels because of inflammation. The normal blood vessels could transport more quickly than damaged blood vessels in the inflammatory sites. In the severe and weak inflammatory sites, they could be separated with CNR changes from time course MRI. Comparing the CNR changes in the inflammatory sites, the CNR values are more decreased in the severe inflammatory sites than in the weak inflammatory sites. In the earlier time, the CNR changes in the severe inflammatory sites were occurred more rapidly than in the weak inflammatory sites. In this case, this phenomenon should be explained with immune cell contents per the unit area, not blood vessels. If there are more infiltrated immune cells, they could engulf the much MNPs per the unit time. So, the different decay times in each inflammatory area could reflect the immune cell contents per the unit area. This means that in vivo MR imaging using MNPs having long blood half-life time could precisely distinguish the degree of inflammation within 12 h. We expect that this method could contribute to diagnosis and monitor the inflammations and therapeutic effect of medicines.

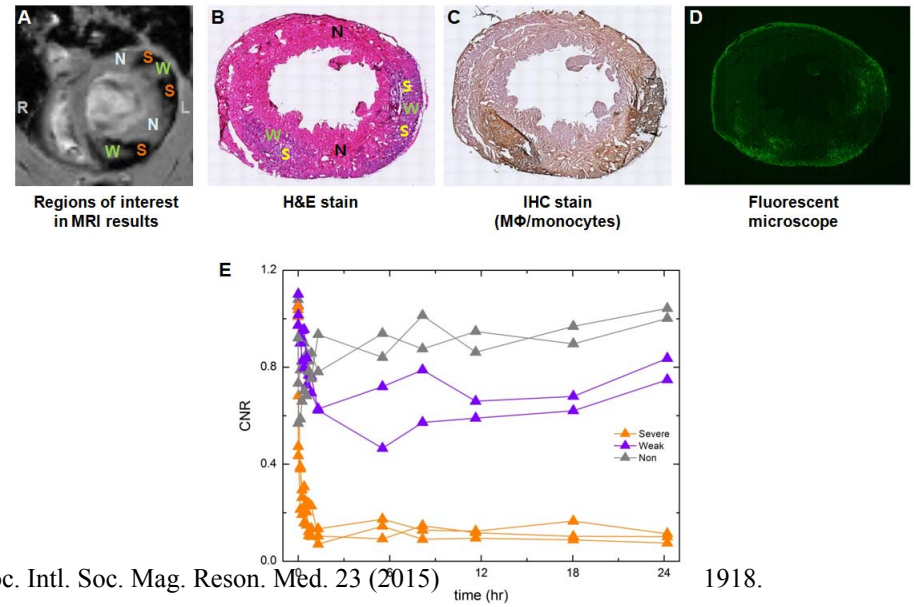

Figure 1. **A, B, C, and E**. The CNR changes in each inflammatory site. We divided the inflammatory regions; no inflammation area (N, and light gray colored triangles), weak inflammation area (W, and purple colored triangles), and severe inflammation area (S, and orange colored triangles). These inflammatory regions were selected from H&E stain, IHC staining results. **D**. Because MNPs are coated with the fluorescent dye, the locations of MNPs are shown with fluorescent microscope images