The Two-pronged Approach for Non-invasive Early Detection of Acute Cardiac Allograft Rejection by MRI in a Rodent Transplantation Model

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INTRODUCTION:

The current gold standard for diagnosing and staging rejection after organ transplantation is biopsy, which is not only invasive but also prone to sampling errors. The goal of this study is to establish cardiac MRI methods for early and non-invasive detection of acute cardiac allograft rejection. We have used the novel two-pronged approach to detect acute cardiac allograft rejection using our rodent transplantation model. First, we use MRI to detect immune cell infiltration at the rejection sites by monitoring the accumulation of dextran-coated ultra-small superparamagnetic iron oxide (USPIO)-labeled immune cells *in vivo*. Second, we establish MRI parameters that are associated with organ dysfunction resulting from acute rejection.

METHODS:

1. Animal model: We developed an abdominal heterotopic working heart and lung transplantation model in rats using DA to BN transplantation pairs. The transplanted hearts exhibited similar cardiac function and output as well as ventricular pressure close to those in native hearts.

2. MRI methods: Cine imaging was used to evaluate cardiac function and USPIO accumulation with the following imaging parameters: FOV = 4cm; resolution=156X156X1500μm^3; TR=a cardiac cycle (about 165 msec); TE= 5.5 msec or 10 msec. Tagging was achieved by a modified DANTE sequence. All MRI scans were performed on Bruker AVANCE 4.7-T system.

3. USPIO labeling: Immune cells, mostly macrophages, are labeled *in vivo* by intravenous injection of USPIO particles 24 hours prior to MRI scans.

RESULTS:

We have previously shown (1) that immune cells, particularly macrophages, accumulated in the rejection sites can be detected non-invasively with MRI by *in vivo* labeling immune cells with USPIO when severe rejection occurred in a non-working heart model. The goal of this study is to detect early rejection before irreversible heart damage happens. In our new heterotopic working heart model, we have found that at earlier rejection state, the accumulation of immune cells is spatially heterogeneous. The immune-cell-concentrated foci can be detected by T_2^*-weighted MRI *in vivo* one day after administration of USPIO (Fig. 1A). Patches of signal reduction are detectable, presumably caused by accumulation of USPIO-labeled immune cells, particularly macrophages.

In addition, mildly to moderately rejected allografts exhibited spatial heterogeneity in contractility and it can be detected by cardiac tagging (Fig1, B&C). The extent of the twist and radial shortening can be quantified by displacement field (Fig.2, B&C) between any 2 cardiac phases. The angles of the arrow heads represent the direction of motion whereas the length of the arrow heads represents the extent of the motion. The anterior portion of the septal wall preserved most of the motility whereas the lateral LV free wall has lost most of the motility. The areas with impaired contractility (lateral wall) revealed by tagging largely correlated with the USPIO-accumulated patches. Moreover, regional wall motion was also measured by cine imaging and analyzed with the centerline method. 100 chords were laid across the LV wall and the length of each chord was tracked at each cardiac phase. Two out of 10 phases are shown in Fig.2E. The chords are sub-grouped according to the sectioning in Fig.2D. The inferior wall (I) and inferioseptal wall (IS) preserved normal thickening pattern where as inferiolateral (IL) and anteriolateral (AL) wall showed abnormal wall thickening. The regional wall motion pattern also correlates with the patches that had significant USPIO-dependant signal reduction.

CONCLUSIONS:

Our data suggest that early rejection is spatially heterogeneous. The immune cell infiltrated foci can be detected non-invasively with *in vivo* USPIO labeling of immune cells whereas the regional functional loss can be measured by tagging and wall motion analysis. The two-pronged approach provides a potential non-invasive diagnostic tool for detecting early acute cardiac allograft rejection.

REFERENCE:

1. Kanno, et. al (2001) *Circulation* **104,** 934-8.

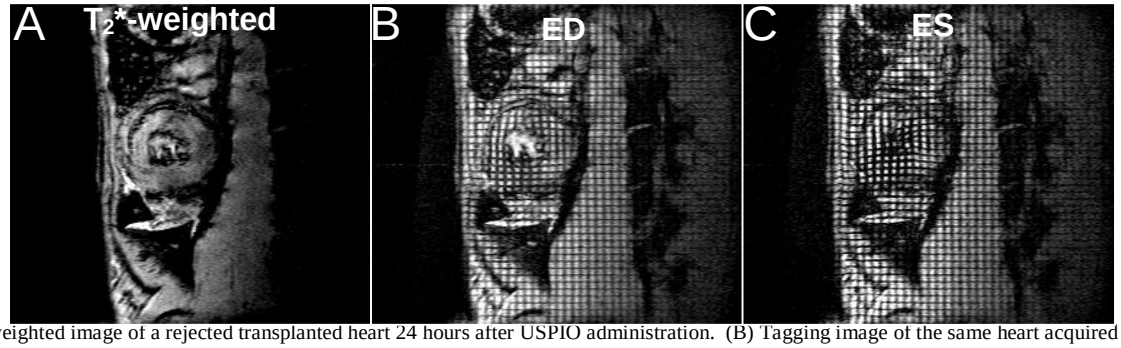

Figure1 (A) T_2^*-weighted image of a rejected transplanted heart 24 hours after USPIO administration. (B) Tagging image of the same heart acquired at end-diastole (ED). (C) Tagging image of the same heart acquired at end-systole (ES).

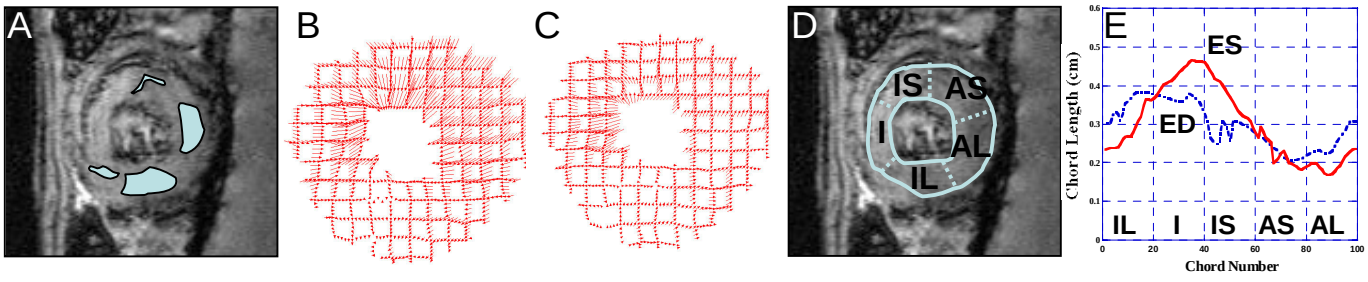

Figure2 (A) Highlighting regions with USPIO-dependant signal reduction. (B) Displacement field between 2 phases in systole. (C) Displacement field between 2 phases in diastole. (D) LV wall sectioning: IL: inferiolateral; I: inferior wall; IS: inferioseptal wall; AS: anterioseptal; AL: anteriolateral wall. (E) Regional wall motion of the LV wall analyzed by the centerline method. 2 cardiac phases shown: red solid line from the end-systole (ES) and blue dotted line from the end-diastole (ED). 100 chords are laid across the LV wall. Chord number one starts at the boundary of AL and IL. The numbering runs in a counterclockwise direction.