Non-invasive Evaluation of Chronic Cardiac Rejection after Heart Transplantation with Multi-parameter Cellular and Functional MRI

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INTRODUCTION: Chronic cardiac rejection (CR) remains the main cause for long-term graft loss and mortality after heart transplantation. The current clinical practice to evaluate allograft rejection is to rely on invasive procedures, such as endomyocardial biopsy for acute rejection surveillance, and coronary angiography or intravascular ultrasound for CR diagnosis (1). These methods are less than ideal because they are not only invasive and costly, but with uncomplimentary information. The goal of this study is to find alternative non-invasive and reliable methods to diagnose CR. We used a heterotopic rodent model of CR to investigate longitudinal characteristics of CR progression over time with multi-parameter cellular and function MRI.

METHODS: An abdominal heterotpic working heart transplantation in rats was used for this study with the natural configuration of pulmonary and coronary circulation is preserved in this mode (2). The graft heart receives sufficient volume and pressure loading and exhibits wall motion close to native hearts (3). Global cardiac function was evaluated with cine MRI at 4.7 Tesla, and regional wall motion and strain were evaluated with tagging MRI and strain analysis using HARP. For cellular MRI, micro-meter sized iron oxide (MPIO) particles are used to label immune macrophages, *in vivo*. The infiltration of labeled macrophage in the rejecting grafts were tracked with *in vivo* T_2^*-weighted imaging at 4.7 Tesla, and confirmed with *ex vivo* MR microscopy at 11.7 Tesla and pathology.

RESULTS AND DISCUSSION: The transplanted grafts are monitored every 2 weeks over the time course of 4 months with *in vivo* MRI. Figure 1 shows T_2^* MRI, tagging and circumferential strain map (Ecc) at 3 time points taken from the same allograft animal for over 80 days. Our preliminary data showed that early CR is heterogeneous. On post-operational day (POD) 47, Slice A shows little or none detectable hypointensity (Fig.1A), whereas the neighboring Slice B already shows some detectable macrophage infiltration in the lateral LV wall (Fig.1G), defined by hypointensity in T_2^* MRI. Interestingly, Slice A shows high Ecc values (Fig.1B) on POD47, which are within the normal ranges of healthy hearts; whereas slice B exhibits some compromised Ecc values in the areas corresponding to detectable hypointensity (Fig.1H). On POD 73, Slice A starts to show some macrophage infiltration (Fig.1C), and the corresponding areas also exhibit decrease in Ecc (Fig.1D). Overall, as rejection progresses over time, both slices gradually showed increase in macrophage infiltration, and although not perfectly mapped, regions with hypointensity largely correspond with decreased Ecc. On POD 81, slice B shows series of hypointensity (Fig. 2A, B) that could be clusters of macrophage-infiltration foci. These areas with hypointensity correlate with single macrophages revealed by MRM at 11.7T (Fig. 2C, D). More systematic longitudinal examination of a larger sample sizes will be carried out in the next grant period to establish clinically relevant indexes for potential clinical translation.

CONCLUSION: Our preliminary results indicated that the chronic cardiac rejection is heterogeneous. The simultaneous cellular and tagging MRI can evaluate rejection status non-invasively over time, which may be a reliable alternative for assessment of CR and potentially translate to clinical arena.

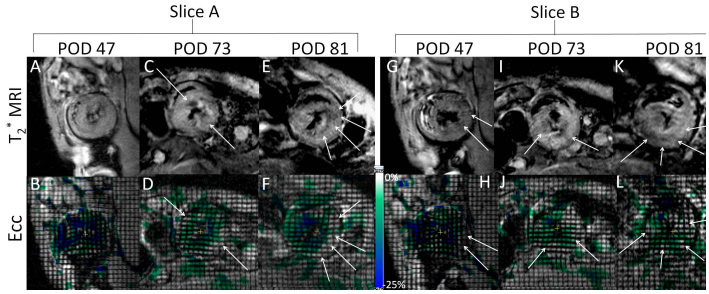

Figure 1 Longitudinal non-invasive imaging of the same allograft heart for T_2^* MRI (top panels) and Ecc, circumferential stain, (lower panels). The white arrows point to areas with detectable hypointensity, and the corresponding areas on the Ecc maps.

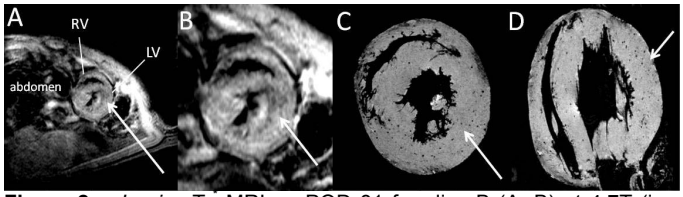

Figure 2. *In vivo* T_2^* MRI on POD 81 for slice B (A, B) at 4.7T (in-plane resolution 156 micrometer, and 1.5 mm slice thickness); and *ex vivo* MR Microscopy (C, D) at 11.7T (isotropic resolution 46 micrometer) for slice B harvest on POD 81. The white arrows point to areas with detectable hypointensity. B is the partially enlarged image from A. C: short-axis view; D: long-axis view. LV: left ventricle; RV: right ventricle.

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