Non-invasive Evaluation of Allograft Rejection after Heart Transplantation with Integrated Cellular and Functional MRI

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INTRODUCTION

Current standard practice for monitoring rejection after heart transplantation is relying on invasive procedures, such as endomyocardial biopsy for acute rejection (AR) surveillance; and coronary angiography, or intravascular ultrasound (IVUS) for chronic rejection (CR) diagnosis. They are invasive and the accuracy is less than ideal. The aim of this study is to establish integrated cellular and functional MRI parameters for various stages of acute and chronic rejection, in searching for possible non-invasive surrogate indicators with MRI that could potentially translate to clinical arena. Various combinations of rodent transplantation pairs are used to mimic different degrees of clinical manifestation of acute and chronic rejections.

METHODS

A. Animal model: A rodent heterotopic working heart and lung transplantation mode in abdomen is implemented for this study. The natural configuration of pulmonary and coronary circulation is preserved; the graft heart receives sufficient volume and pressure loading and exhibits wall motion and strains close to those of native hearts. Various transplantation combinations of different inbred rat strains are used to mimic different degrees of AR and CR with different time courses. DA-to-BN allograft hearts develop AR within a week after transplant surgery without developing into CR; Lewis-to-Fisher combination had less severe AR within a month after transplantation and gradually develops CR after 2 months; whereas PVG1U-to-PVGR8 transplantation pairs develop CR with little or none detectable AR, and CR becomes evident after post-operational day (POD) 100.

B. MRI methods: Micro-meter sized iron oxide particles (MPIO) are used to label immune cells *in vivo* and the labeled cells are tracked over time with T_2^* MRI. Cine MRI is used to access global systolic functions, whereas tagging MRI followed by strain analysis is used to assess regional ventricular wall motion abnormality. Real-time first-pass dynamic contrast with Gd-based contrast agent is used to access myocardial perfusion. Delayed enhancement (DE) with Gd is used to evaluate myocardial viability and scaring. Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) is used to evaluate potential tissue remodeling.

RESULTS

Rejecting allograft hearts showed differential myocardial perfusion across LV (Fig.1), with affected regions showing retarded contrast enhancement (Fig.1B&D, white arrows) with slower wash-in kinetics (Fig.1E, red triangles). The areas with decreased myocardial perfusion also exhibited compromised wall motion and strains (Fig. 2 A&B) detected by tagging MRI, and hypointensity upon MPIO labeling, indicating macrophage infiltration (Fig. 2 C&D). Similarly, allograft hearts with CR showed heterogeneous manifestation of hypointensity, which are foci MPIO-labeled macrophage infiltration (Fig. 3 A&B). Areas with more macrophage infiltration showed compromised wall motion and strains (Fig. 3 C&D). PVG chronically rejected hearts after almost 4 months after transplantation did not show significant changes in water density and DWI (Fig. 4 B), but some changes in DTI (Fig. 4D), indicating possible myocardial remodeling (Fig. 4).

CONCLUSION

Our data indicated that the allograft rejection, both AR and CR, appears to be highly heterogeneous. Regions with compromised functions also show more macrophage infiltration. Multiple MRI parameters provide further accuracy in rejection evaluation. Detailed profiling and modeling of the temporal and spatial relationship of the integrated multi-parameter MRI may be useful in establishing surrogate markers for various stages of rejection that can compliment current invasive procedures.

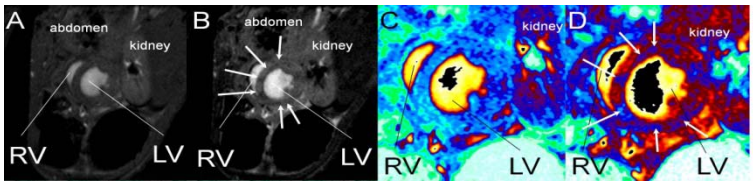

Figure 1 First-pass dynamic imaging of a DA-to-BN allograft heart on POD 5. (A, C) Pre-contrast (B, D) After Gd, (C,D) A and B colored and partially enlarged (E) temporal signal changes of different heart regions, showing red as the affected septal wall.

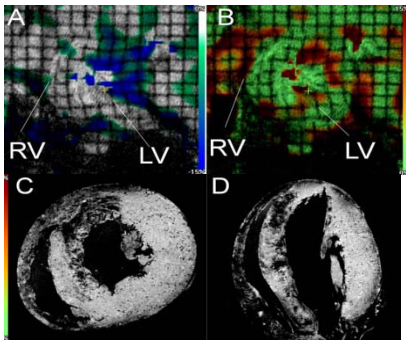

Figure 2 (A) Circumferential stain (Ecc), (B) radial strain (Err), and (C, D) T_2^* MR microscopy of Fig.1 allograft.

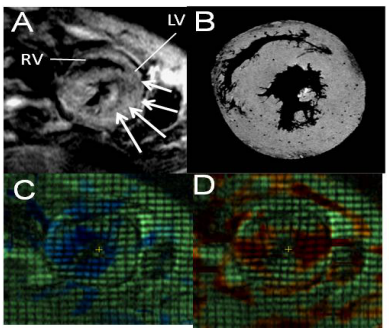

Figure 3 (A) *In vivo* T_2^* MRI (B) *Ex vivo* T_2^* MR microscopy (C) Circumferential stain (Ecc), (D) radial strain (Err) of a chronically rejected PVG allograft heart on POD 81.

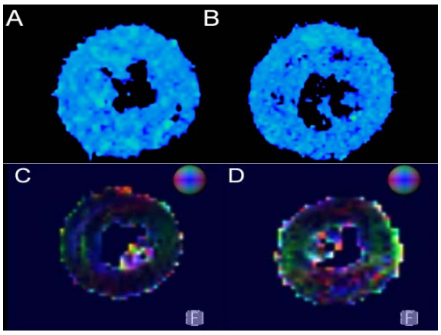

Figure 4 Diffusion-weighted imaging (A, B), and diffusion tensor imaging (C, D) of a control heart (A, C) and a chronic PVG allograft heart (B, D) harvest on POD 112.