MRI characterization of cardiac tissue scaffold materials in vitro and in vivo

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Background: Grafting of tissue scaffolds containing stem cells onto the infarcted heart may improve cardiac function by reducing wall stress, increasing stem cell retention and regenerating scar tissue (1-3). Scaffold composition can be partially optimised *in vitro*, but the true test of a scaffold is *in vivo* performance. Here, we used MRI to detect cardiac scaffold materials grafted onto rat hearts and to measure the effect of the applied scaffold on cardiac function

MRI Methods: MRI was performed using a vertical-bore, 500 MHz, 11.7 T MR system with a Bruker console running Paravision 2.1.1. 3D-MR-microscopy used a 40-mm quadrature-driven birdcage coil (Rapid Biomedical) and a fast gradient echo sequence (TE/TR = 1.8/15 ms; 15° pulse; field of view, 32 × 32 × 64 mm; matrix size, 512 × 512 × 512; voxel size, 32 × 32 × 64 µm). Cardiac morphology and contraction were measured from a stack of contiguous 1.5-mm true short-axis ECG and respiration-gated cine-MR images using a 52-mm quadrature-driven birdcage coil (Rapid) and FLASH sequence (TE/TR, 1.43/4.6 ms; 17.5° pulse; field of view, 51.2 × 51.2 mm; matrix size, 256 × 256; voxel size, 200 × 200 × 1500 µm; 25 to 35 frames per cardiac cycle). First-pass perfusion was imaged used a fast gradient echo sequence that acquired one mid-papillary short axis image per heart beat during bolus injection of 0.5mg/kg Gd-DTPA (TE/TR, 0.8/2 ms; 60° pulse; field of view, 40 × 40 mm; slice thickness, 1.5 mm; matrix size, 64 × 64, zero filled to 256 × 256). Delayed enhancement imaging was performed 15 minutes post Gd-DTPA infusion using cine MRI with increased flip angle to saturate signal in viable myocardium.

Results: We used *in vitro* and *in vivo* MRI to assess three cardiac scaffold materials, poly(ethylenetephatalate)/dimer fatty acid (PED), TiO_2 reinforced PED and poly(glycerol sebacate) (PGS). PED and TiO_2-PED scaffolds were grafted onto control rat hearts. One week later, hearts were excised and underwent 3D-MR-microscopy. Scaffold material was identified as signal voids on the outside of the heart. PED scaffolds became fractured by the stress of repeated cardiac contraction, while TiO_2-PED remained intact (*Figure 1*).

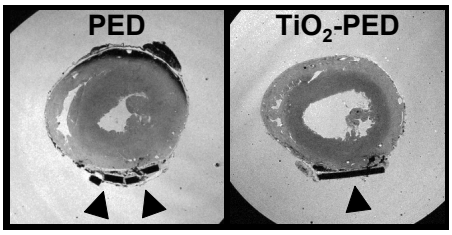

Figure 1: 3D-MR microscopy images showing fractured PED and intact TiO_2-PED scaffolds on the epicardial surface of hearts excised 1 week after grafting

TiO_2-PED and PGS scaffolds were then grafted onto infarcted rat hearts, while control rats underwent infarction without scaffold grafting. After 1 and 6 weeks *in vivo* MRI was performed. At 1 week, scaffolds were visible on *in vivo* cine-MR images and cardiac function was not significantly different between groups (*Figure 2*). However, first pass Gd-DTPA perfusion imaging and delayed enhancement MRI indicated extensive microvascular obstruction and necrosis adjacent to the TiO_2-PED scaffold (*Figure 2*). At 6 weeks, cardiac function was maintained in the control and PGS groups, but deteriorated in the TiO_2-PED group with ejection fraction reduced from 41 to 36% (*Figure 2*). TiO_2-PED scaffolds remained visible at 6 weeks. However, the PGS scaffolds, previously shown to retain stability for several months *in vitro* (1), degraded almost completely (*Figure 2*).

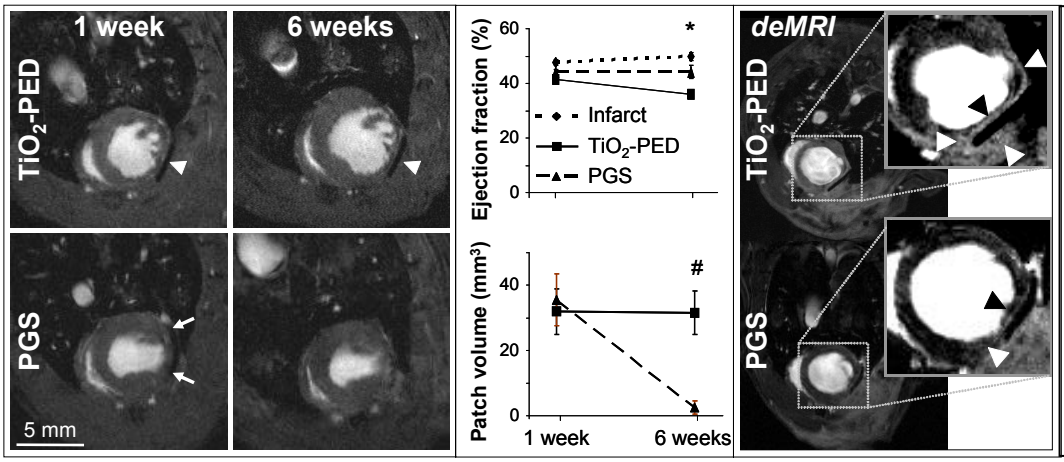

Figure 2: ***Left****; in vivo* MRI showing TiO_2-PED and PGS scaffolds (arrows) attached to the epicardial surface of infarcted rat hearts 1 and 6 weeks after grafting. Note that by 6 weeks the PGS scaffold is no longer visible: ***Top-Middle***, ejection fraction of control infarcts, TiO_2-PED and PGS grafted hearts at 1 and 6 weeks after grafting. ***Bottom–middle,*** scaffold volume at 1 and 6 weeks after grafting: ***Right,*** delayed enhancement MRI performed at 1 week showing extensive areas of hyper-enhancement adjacent to the TiO_2-PED tissue scaffold, signifying tissue necrosis.

Conclusions: We show that MRI can be used to identify cardiac scaffold location and degradation *in vitro* and *in vivo*, and can yield data essential for the optimisation of cardiac scaffold material design. This particular study demonstrated that TiO_2-PED is not suitable for cardiac scaffolds, as its rigidity caused tissue necrosis and reduced perfusion adjacent to the scaffold, resulting in reduced heart function. PGS scaffolds were not detrimental to function and may provide a suitable base material for engineering heart tissue. Further, degradation of scaffold material was more rapid *in vivo* than predicted by *in vitro* testing (1), highlighting the importance of using non-invasive imaging to optimise myocardial tissue engineering.

1) Chen QZ, *et al*. **Biomaterials**. 2008;**29**:47. 2) Zimmermann WH,*et al*. **Nat Med.** 2006;**12**:452. 3) Jawad H, *et al*. **Br Med Bull**. 2008;**87**:31.