MRI visible bioscaffold for stem cell-mediated repair and improved cardiac function

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Target Audience: The work presented in this abstract is of interest researchers studying myocardial regeneration therapies, cardiologists and pre-clinical multi-modal imaging; specifically functional cine-tagged MRI and diffusion tensor MRI.

Purpose: To assess the therapeutic value of transplanted bone marrow mononuclear cells on cardiac function following ischemic injury in rats using high-field MRI.

Introduction: The severely limited ability of the heart to repair itself following injury has led to the development of a number of novel cell therapies aimed at stimulating myocardial regeneration [1]. Transplanted bone marrow mononuclear cells (BMCs) are proposed as one such solution owing to their ability to promote myocardial survival and neovascularisation through secretion of paracrine factors, reducing infarct size [2]. However it is difficult to assess the efficacy of this treatment as the fate of therapeutic cells is uncertain and the majority are lost from the injection site within minutes of delivery, largely due to myocardial contraction expelling the cells. A visible cardiac patch that delivers cells within a nurturing biomaterial offers the promise of a significant improvement in the efficacy of stem cell-mediated regeneration by increasing cell engraftment and survival, and improving post-infarct remodelling and cardiac function. This study aimed to use in-vivo imaging to determine the success and location of intra-myocardial injections of therapeutic BMCs in a visible hydrogel, and combine these data with tag-cine MRI to correlate the presence of grafted MNCs to changes in regional myocardial contractility.

Methods: Bone marrow was extracted from adult Wistar rat hind-limbs, BMCs were isolated by centrifugation, then suspended at 10^7 cells/ml in 100µl gadolinium doped alginate hydrogel for each injection. Myocardial infarction was induced by ligation of the left anterior descending artery. BMCs were either directly injected into the ischemic region during surgery (n=3) or injected closed chest using ultrasound guidance at one week after infarction (n=3) (fig. 1).

***Imaging*:** Cardiac and respiration gated MRI was performed 3 days after cell injection at 9.4T (Agilent Technologies Inc., CA, US) with 40 G/cm gradients and a 72mm transmit coil with a 4-channel receive array (Rapid Biomedical). First a short axis cine-stack covering the whole LV (0.4x0.4x1.5mm; FA 10°; TE/TR 1.2/5ms) was acquired to measure left ventricular properties. A pre-contrast inversion recovery (IR) sequence was performed to locate Gd-doped cell encapsulating hydrogel deposits (0.27x0.27x1.5mm; TE/TR/TI 1.6/3.9/~500ms). Fifteen minutes after intraperitoneal injection of 0.5mmol/kg Gd-DTPA, a post-contrast inversion recovery sequence was acquired to measure infarct size. The final acquisition was a high resolution DANTE tagged cine sequence to measure regional cardiac contraction (0.2x0.2x1.5mm; 0.3mm tag spacing; analysed with inTag©(CREATIS, Université Lyon, FR)).

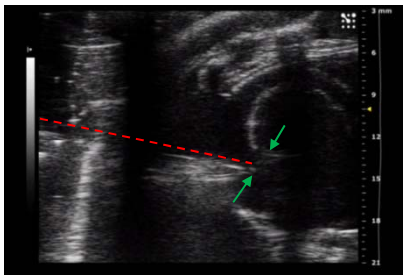

Fig 1. Snapshot from ultrasound guided injection. Red line runs parallel to needle echo and green arrows define the epi/endocardial border.

Results: The Gd-enhanced bioscaffold was readily visible on the pre-contrast image, demarcating the region of cell therapy administration in the myocardium (2a). Following Gd contrast, the area of ischemic myocardium enhanced demonstrating good co-localisation of the therapy and the damaged tissue (2b). Combining this information with tag-cine MRI permits the presence of grafted cells to be correlated with changes in regional circumferential and radial strain, allowing the local effect of therapy on myocardial contractility to be determined (fig2c). Although this study is not currently powered to identify improvements in function, the data in table 1 suggest a small improvement in ejection fraction and stroke volume in treated hearts.

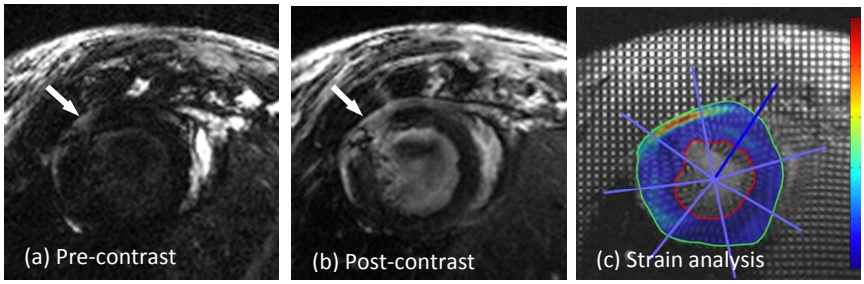

Fig 2 .Representative images from chronic infarct + treated rat. The pre contrast image shows the location of Gd-doped and cell enriched alginate (a) while the post Gd image defines the infarcted myocardium (b) strain analysis shows positive strain (tissue stretching) at infarct (c).

Table 1. Global cardiac function

	Infarct no treatment	Infarct + BMCs	Chronic infarct + BMCs
Ejection fraction (%)	59 ± 3	73 ± 14	67 ± 4
LV Mass (mg)	698 ± 22	739 ± 17	716 ± 73
Stroke Volume (µL)	285 ± 26	399 ± 82	412 ± 45
Infarct mass (mg)	105 ± 30	63 ± 25	77 ± 10
Infarct volume (%LV)	15.7 ± 5.0	8.5 ± 3.3	10.9 ± 1.2
Pre-contrast hydrogel volume (%infarct)	-	29 ± 14	35 ± 17

Discussion: This work establishes a method for visualising implantation and assessment of BMCs as a regenerative cardiac therapy in rats using MRI by confirming the presence of cellular bioscaffold, quantifying infarct size and measuring regional function to directly assess therapeutic success. This imaging strategy has applications in the improving evaluation of all cardiac regeneration strategies using cell transplantation, in which the positive or negative impact of cells on their local myocardial environment is not well known.

References: [1] Coulombe, K., Bajpai, V.K., Andreadis, S.T. & Murry, C.E. Annual review of biomedical engineering (2014); [2] Kamihata, H. et al. circulation 104, 1046–1052 (2001)