Dynamic Contrast-Enhanced MRI Assessment of Vascularity in a Regenerative Tissue Matrix

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Introduction: Regenerative tissue matrix is widely used to enhance healing after breast reconstructive surgery and hernia repair[1,2]. Vascularization is a critical element of enhancing tissue repair with tissue matrix because a blood supply is needed to support tissue regeneration. Dynamic contrast-enhanced MRI (DCE-MRI) is widely used to quantify changes in vascularity in the setting of cancer progression and cancer treatment[3] and has shown promise for assessing vascularity in tissue matrix for bladder reconstruction[4]. We tested the hypothesis that DCE-MRI could noninvasively quantify serial changes in vascularity over time after subcutaneous implantation of a regenerative tissue matrix.

Methods: Nude mice (n=14) underwent subcutaneous tissue matrix implantation (AlloDerm, LifeCell, Bridgewater, New Jersey USA), with sheets sized 50x50x1 mm implanted in the dorsum between the shoulder blades. MRI was performed on day 2 (designated week 0) and weeks 1, 2, 3, and 4 after implantation, with n=6 mice per time point. These time points were chosen to provide a range of vascular responses. Imaging was performed on a 7T Bruker Clinscan small animal imaging system. Mice were anesthetized with 1.25% isoflurane, and body temperature was maintained between 36-37°C using circulating warm water. An indwelling tail vein catheter was established to inject Gd-DTPA. Gadolinium-enhanced DCE-MRI was performed to assess vascularity. A dual bolus Gd-DTPA injection scheme was used, with a 0.033 mmol/kg dose to acquire the arterial input function (AIF) in the left-ventricular cavity and a 0.1 mmol/kg dose to acquire the tissue function (TF) in the implant. To acquire the AIF, the left ventricle was imaged using an ECG-gated gradient echo saturation recovery sequence with the following parameters: images=400, NEX=1, TR/TE=1.6/0.8 ms, resolution=.47 x.47 x1.0 mm, FOV = 30x14 mm, saturation delay = 10ms, excitation flip angle = 25°, and acquisition time/image = 64 ms. To acquire the TF, an axial section of the AlloDerm implant was imaged using the same pulse sequence, but with respiratory gating and the following imaging parameters: images=400, NEX=4, TR/TE=2.0/1.1 ms, resolution=.195 x.195 x1.0 mm, saturation delay = 200ms, excitation flip angle = 25°, and acquisition time/image ≈ 1 s. AIF and TF curves were generated from regions of interest on DCE-MRI images, and were analyzed using a Kety model[5], yielding an estimate of K_{trans} in ml/g tissue/min. K_{trans} from chest wall skeletal muscle was used as a control. Animals were sacrificed weekly (N=1, 1, 2, 5, 5 at weeks 0 to 4, respectively) and histology was performed using hematoxylin & eosin to stain for blood vessels. The total number of vessels observed in the implant was calculated from histology images to serve as an index of vascularity.

Results: Figure 1B,C shows example DCE-MRI images taken from a mouse 2 weeks after AlloDerm implantation. Figure 2 demonstrates increasing K_{trans} over time in the tissue matrix ($p < .05$ for weeks 3 and 4 vs. weeks 0 and 1 via Tukey test), noninvasively quantifying the development of a vascular bed over the course of several weeks in the implanted construct. K_{trans} in skeletal muscle was unchanged at each time point. Vessel counts obtained from histological slices are shown in Figure 3. While statistical significance was not achieved for vessel count data due to small sample size, the shape of the curve in Figure 3 supports the hypothesis that vascularity increased in the implants during the course of this study.

Conclusions: DCE-MRI with K_{trans} analysis noninvasively quantified increasing vascularity in tissue matrix after implantation. This technique promises to be useful for evaluating changes in vascularity over time in novel tissue matrix formulations that aim to modulate angiogenic activity.

References: 1). Salzberg CA, *Ann Plast Surg* 2006. 2). Buinewicz B and Rosen B, *Ann Plast Surg* 2004. 3). Wedam SB et al, *J Clin Oncol* 2006. 4). Cheng HL et al *J Magn Reson Imaging* 2005. 5). Tofts PS et al, *J Magn Reson Imaging* 1999.

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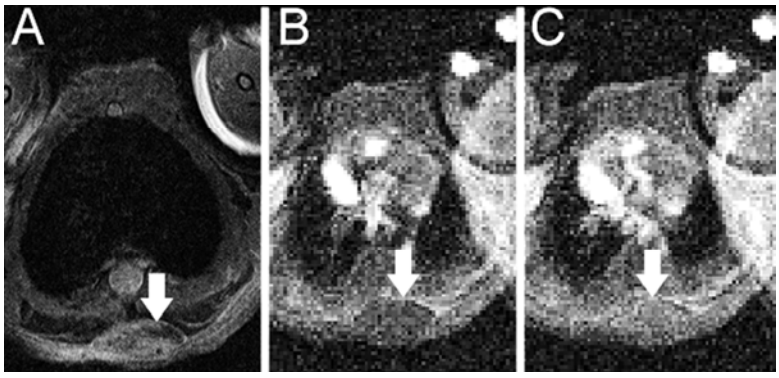

Figure 1: Example DCE-MRI images of a mouse 2 weeks after implantation of tissue matrix. (A) High resolution anatomic reference image. (B) before contrast injection and (C) at peak concentration in the AlloDerm implant. *White arrows* indicate the location of the implant.

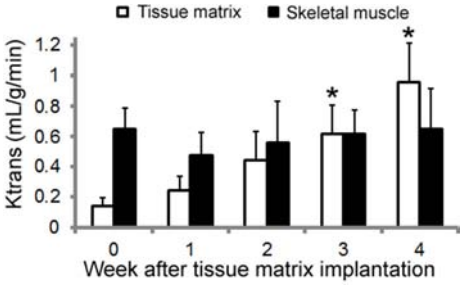

Figure 2: Comparison of K_{trans} in implanted tissue matrix *(white)* and skeletal muscle *(black)*. *p<0.05 vs. weeks 0 and 1.

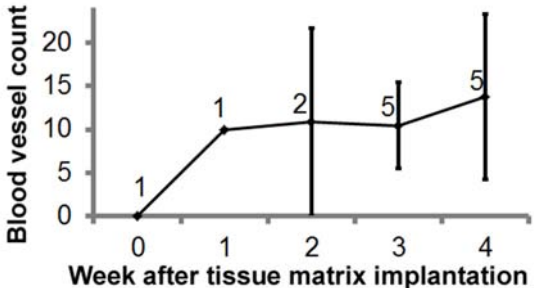

Figure 3: Vessel counts in tissue matrix implants determined from histology, with the number of samples analyzed indicated next to the data points.