Using ^{19}F MR to monitor delivery and engraftment of therapeutic stem cells *in vivo*: accuracy evaluation

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Introduction:

Mesenchymal stem cells (MSCs) are a promising cell therapy to induce arteriogenesis for Peripheral Artery Disease (PAD) patients. However, non-invasive serial monitoring of cell delivery and engraftment is problematic. Cellular encapsulation with alginate-poly-L-lysine-alginate (APA) loaded with perfluorooctylbromide (PFOB) may provide a means to monitor therapy by both MRI and c-arm CT using standard clinical scanners. Compared to c-arm CT, ^{19}F MRI tracking is advantageous due to the lack of ionizing radiation and high sensitivity owing to the absence of native fluorine in the body. However, MRI suffers from lower spatial resolution than X-ray angiography. The purpose of our study is to evaluate the accuracy of non-invasive *in vivo* tracking of encapsulated MSCs using ^{19}F MRI relative to c-arm CT.

Methods:

MSC Microencapsulation and Delivery

APA-PFOB microcapsules containing MSCs were produced using a static droplet generator. New Zealand White rabbits (n=7) received 6 intramuscular injections of 500 microcapsules per injection in the medial thigh.

In vivo ^{19}F MR and C-arm CT Imaging

Imaging was performed at 1-14 days after injection to monitor delivery and engraftment of encapsulated MSCs. The animals were anesthetized and placed supine for imaging in a 3T clinical scanner (MAGNETOM Tim Trio, Siemens) and X-ray angiographic system (AXIOM Artis dFA, Siemens). Scout proton MRIs were acquired using the body coil for localization followed by proton shimming. A custom 4-channel phased array fluorine coil was placed anteriorly and tuned to the triplet peak from PFOB. Three-dimensional volumes were obtained using a steady-state free precision pulse sequence (TrueFISP) using the following parameters: 3.9/2.0ms TR/TE; 1.5x1.5x2 mm voxel size; 32 averages; 1002 Hz bandwidth; and 14 min scan time. A c-arm CT was acquired either immediately prior to or after MRI using the following parameters: 8s rotation; 240º scan angle; 0.5º increment; 0.36 µGy dose per pulse; and 0.31 mm^3 voxel size.

Image Processing and Analysis

The c-arm CT images were segmented using an automatic thresholding algorithm to identify the APA-PFOB injection sites (Fig. 1a). Optimal thresholds were determined by Otsu's histogram method, which minimizes the intra-class variance, to form binary images. C-arm CT images were then registered to ^{19}F MR images using a custom 3D registration software (Dextroscope) (Fig. 1c). The volume of each injection site calculated from the thresholded images was analyzed for possible correlation between imaging modalities. The center of mass (COM) of each injection site was determined as the mean position of the constituent voxels weighted by intensities. Registration offset was estimated as the linear distance between COMs of each paired ^{19}F MRI and c-arm CT injection sites (Fig. 1d).

Results:

A similarly high percentage of injection sites were identified on MRI (100% of 42) as on CT (100% of 42). A high concordance was observed in the spatial locations and volumes of the injection sites between ^{19}F MRI and c-arm CT. The mean offset between COMs at each injection site between MRI and CT was 0.43±0.16 mm. The injection site volumes were highly correlated between MRI and c-arm CT ($r=0.92$, $p<0.05$, Fig. 1e).

Conclusions:

Small offset between two modalities and minor discrepancies in volume measurements were observed that are probably caused by differences in animal positioning and partial volume effects, i.e., the spatial resolution of the ^{19}F MRI is approximately 5 times lower than c-arm CT. The high identification and agreement in the spatial locations and volumes of the injection sites between ^{19}F MRI and c-arm CT demonstrated that ^{19}F MRI provides an accurate alternative to c-arm CT for the identification of APA-PFOB microcapsules containing stem cells. Thus, ^{19}F MRI is an attractive non-invasive method for tracking of stem cell therapies *in vivo* without ionizing radiation.

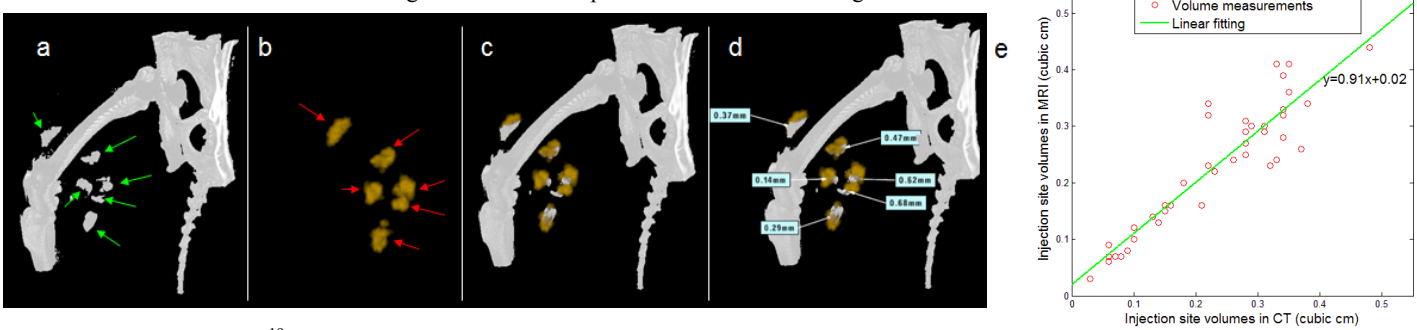

Fig. 1 a) c-arm CT and b) ^{19}F MR images after thresholding reveal six injection sites of PFOB capsules (arrows). c) Co-registered images show a high concordance. d) Registration offset is small between COMs of each paired ^{19}F MRI and c-arm CT injection sites. e) Injection site volume measurements between CT and MRI show a high agreement.