MR-guided delivery of magnetoencapsulated pancreatic islets in a swine model

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Introduction: Recent advances in islet cell transplantation for type I diabetes mellitus have provided insulin independence in patients by the successful engraftment of pancreatic islet cells. Given the advances in isolation and purification of islet cells, the next vital steps for therapeutic development include the safe and targeted delivery of these agents and effective means of preventing graft rejection. The current percutaneous method of islet cell transplantation employs fluoroscopic guidance to puncture the portal vein. As this procedure has seen a high rate of complications (15-20%)[1] other methods of delivery are desired. To this end, we have developed a novel transvenous targeted delivery procedure for the delivery of human islets in swine using an MR-trackable needle[2]. Further, to track human islets after delivery and prevent their rejection in the swine host we have developed novel magnetocapsules that are both MR-trackable and capable of immuno-isolating xenogenic grafts. The synthesis of magnetocapsules is based upon the well-characterized protocol for preparing alginate-PLL microcapsules[3]. To the core alginate layer of these microcapsules we have added Feridex® (an FDA-approved SPIO formulation in an off-label application) thus creating an MR-trackable graft. Here we present clinically applicable magnetoencapsulation of human islets and demonstrate the MR detectability of magnetocapsules after intraportal delivery in swine via an MR-guided transvenous delivery procedure.

Methods: Human islets were first suspended in a stock solution of 2% FDA-approved Protonal HD alginate with 20% vol/vol Feridex added. This mixture was then extruded through an electrostatic droplet generator. The resulting microspheres were transformed to alginate microcapsules by subsequent incubation in 100 mM $CaCl_2$, then PLL, and finally alginate. Following magnetoencapsulation, viability of human islets was determined by a microfluorometric assay in which viable cells were labeled with Newport Green and dead cells with propidium iodide. The insulin secretory response of magnetoencapsulated islets was also compared against non-treated islets using a commercially available ELISA. The next step was targeted delivery of magnetoencapsulated islets in swine (n=4 animals). All *in vivo* imaging was performed on a 1.5 T MR scanner (CV/i, GE Medical Systems Waukesha, WI). Images were acquired using a combination of external phased array coils and an MR-trackable intravascular needle. After deep sedation of swine, a standard clinical 12 F sheath was placed in the common femoral vein and the MR-trackable needle was introduced. Using a real-time FIESTA sequence (3.4 ms TR, 1.2 ms TE, 45º flip angle, 125 kHz bandwidth, 10 mm slice thickness, 30 cm FOV, 128 x 128 image matrix, and 1 NEX) in combination with an interactive scan plane acquisition (i-Drive, GE), the needle was advanced into the IVC. Under real-time FIESTA sequence with multiplanar views, the needle system was guided through the IVC and into the portal vein (Fig 1A). A solution of 25% Gd-DTPA was infused to confirm placement in the portal vein and then a nitinol wire (.018") was advanced (Fig. 1B). Once in place, an 8 F catheter was advanced under MR into a branch of the portal vein for infusion of 10,000 magnetocapsules. Following delivery, magnetocapsule distribution was assessed using a combination of external phased array coils and three different pulse sequences : FSPGR (TR/TE: 3.5/1.2 ms, flip angle: 45°), FSE (TR/TE: 1000/11.0 ETL 12) and FIESTA (TR/TE: 8.6/3.6).

Results: The viability and insulin secretory response of magnetoencapsulated human islets was not found to differ from controls over a two-week period in culture. Further, MR-guided puncture and catheterization of the mesenteric venous circulation was accomplished without complication. Active tracking of the catheter allowed for targeted delivery of the magnetocapsulses into the liver segment of choice. On all sequences, magnetic susceptibility-induced signal voids were noted representing the distribution of the capsules in the liver. When administered in the main portal vein, the distribution was predominately in the periphery of the liver with central sparing, which correlates with normal vascular flow patterns in the portal vein. FSPGR acquisition provided the best resolution with clear delineation of the magnetocapsules and their distribution (Fig. 2).

Discussion: The liver, being highly vascularized, appears to be an ideal site for transplantation of microencapsulated islets. To the best of our knowledge, this is the first direct transplantation of microencapsulated islets via portal infusion in swine, an animal whose larger vasculature more closely resembles that of humans. Here we have shown the ability to effectively deliver and image magnetoencapsulated human islets in swine without complications completely under MR guidance. Our magnetocapsule approach is clinically translatable (as FDA-approved compounds are being used) and may further improve islet cell transplantation detection and survival in translational research.

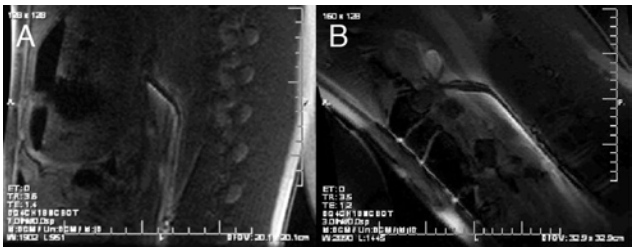

Figure 1: (A) MR-guided puncture of the portal vein with active needle. (B) Catheterization of the vein using a nitinol wire.

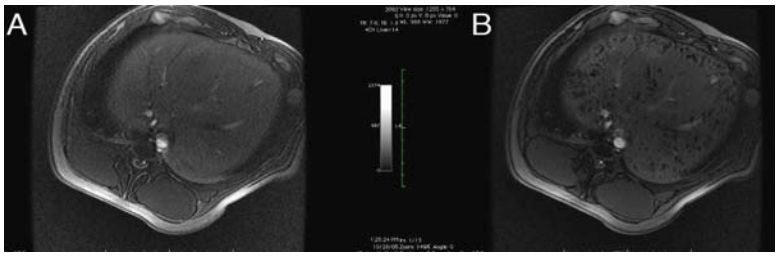

Figure 2: Pre (A) and post (B) images of the liver after delivery of magnetocapsules SPGR (TR/TE: 3.5/1.2 ms, flip angle: 45°).

References: 1) Venturini M et al. Radiology, 2005. 234: 617-24. 2) Arepally A et al. Journal of Magnetic Resonance Imaging. 21:463-7. 2005. 3) Lim F et al., Science. 210, 908-910, 1980.