

## **XFM-Guided Approach to Intrapericardial Delivery of Cardiac Therapeutics**

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### **Background & Purpose**

Current delivery methods for implanting cellular therapeutics in the heart include direct intramyocardial injection (transepical or transendocardial), intracoronary infusion and systemic infusion techniques. However, shortcomings exist for each including leakage of cells from injection sites, loss of cells to systemic circulation, cell death due to ischemia, anoikis and inflammatory processes, and induction of conduction abnormalities.<sup>1,2</sup> Alternately, an intrapericardial (IP) injection would enable stem cells to persist long-term in close proximity to the heart without experiencing these shortcomings. Pericardial approaches to the epicardium have been successfully conducted for delivery of cardioactive drugs, cardiac ablation techniques and implantation of cardiac pacemakers. Presently, no published reports describe utilization of the pericardial space for delivery of stem cells. Conventional use of ultrasound and fluoroscopy provide limited visualization for an IP approach to stem cell delivery (Fig. 1A). X-ray fused with magnetic resonance imaging (XFM) could exploit the strengths of both imaging modalities allowing direct assessments of myocardium and vasculature with real-time interactivity. Further, through use of a novel x-ray visible alginate microcapsule, cells can be tracked with x-ray modalities.<sup>3</sup> Collectively, these elements could aid physicians in delivering therapeutics while reducing radiation exposure time for the patient. The purpose of this study was to determine the feasibility and outcomes of an XFM-guided IP approach for delivery of barium-alginate microcapsules—a radiopaque vehicle for allogeneic mesenchymal stem cell implantation.

### **Materials & Methods**

Synthesis of barium-alginate microcapsules (BaCaps) was done with modification of the classic alginate/poly-L-lysine (PLL)/alginate (APA)<sup>4</sup> microencapsulation protocol using a 10% (w/v) barium concentration.<sup>3</sup> Yorkshire pigs, 40-50 lbs, were studied (n=4 acute studies; n=2 chronic) with XFM-guidance and one chronic study without XFM. For chronic studies, one animal received BaCaps and the other received naked human mesenchymal stem cells (hMSCs). Breath-hold short-axis trueFISP ECG-gated cine MR (TR=25.48; TE=1.59; 280x245 cm FOV; 192x192 image matrix; 6 mm slice thickness; 80° flip angle, 7 segments) images were acquired on a 1.5T scanner (MAGNETOM Espree, Siemens Healthcare, Germany) followed by whole heart 3D TrueFISP navigator-gated cardiac MR (209 ms TR; 1.6 ms TE; 320x240 mm FOV; 256x172 image matrix; iPAT=2; 2 mm slice thickness, 64 slices) and cardiac-gated c-arm CT (syngo DynaCT, AXIOM Artis dFA, Siemens Medical Solutions, 190° rotation; 0.5° angle; 20s acquisition; 48 cm FOV; 3 ml/s iohexal via cardiac catheterization). After 3D-3D registration of MRI and c-arm CT, a segmented MRI of the epicardial and endocardial surfaces was volume-rendered and overlaid with the c-arm CT (Fig. 1B) and live X-ray fluoroscopic imaging (syngo InSpace 3D/3D Fusion, Siemens Medical Solutions). For pericardial access, we used a percutaneous subxiphoid approach under XFM-guidance (syngo i-Pilot, Siemens Medical Solutions) to place a 17 G Touhy needle. Fused segmented cardiac MRI and c-arm CT were used to determine myocardial boundaries and avoid coronary vasculature, respectively. The epidural needle was exchanged over a guide wire for a 4F introducer sheath followed by a 7-10cc IP injection of barium-alginate microcapsules or naked hMSCs. Cardiovascular function and pericardial integrity were assessed in animals surviving 7 days using cine MR imaging and/or M-mode echocardiograms. C-arm CT was performed on chronic study subject having received radiopaque microcapsules to determine persistence of the capsules. Upon humane sacrifice, heart, pericardium and microcapsules were harvested for histology.

### **Results**

XFM-guided IP delivery of therapeutics was successful in 5 of 6 pigs; a single pig went into cardiac arrest prior to IP puncture during cardiac catheterization. BaCaps were easily visualized on acute and chronic C-arm CT studies. In acute studies, BaCaps were freely floating in the pericardial space. In the chronic XFM-guided study, BaCaps formed into a tissue-like patch on the epicardial surface without gross morphological changes to the heart. Histologically, the myocardium had mild inflammation and fibroblastic cells in areas adjacent to BaCaps. Left ventricular ejection fraction was preserved in this animal (LVEF=64.9%). An inadvertent puncture of the left ventricle occurred during the blind puncture, e.g., non-XFM, chronic study, which resulted in adhesions/pericardial thickening seen on MR follow-up (Fig. 1C) and post-mortem. LVEF was reduced to 45.6%, at 1 week follow-up. XFM-guided IP delivery of hMSCs did not produce gross changes to the pericardium. However a 1cm, apical area of pale discoloration was observed grossly. MR follow-up (Fig. 1D) confirmed lack of pericardial adhesions and preserved LVEF.

### **Discussion & Conclusions**

A XFM-guided IP approach to delivery of barium-alginate microcapsules is technically feasible and accurate in a swine model. XFM-guidance offers a method to increase accuracy and safety of the delivery of intrapericardial therapeutics. A good biocompatibility profile for IP delivery of barium alginate microcapsules is suggested through short-term follow up.

### **References**

- 1) Reinecke and Murry. 2002.
- 2) Menasché, et al. 2003.
- 3) Barnett et al. 2006.
- 4) Lim and Sun. 1980.

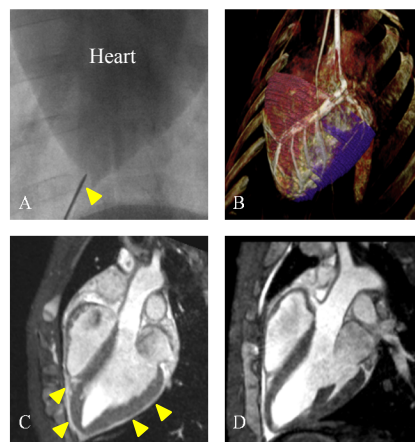


Fig. 1: (A) An X-ray fluoroscopic image demonstrates the poor ability to determine the needle position (arrow) within the pericardial space. (B) XFM of the heart showing ventricular boundaries and coronary vasculature. Follow-up MRI after IP injection of BaCaps showing (C) pericardial thickening (arrows) after blind injection vs. normal pericardium (D) with XFM guidance.