

Intrapericardial Delivery of Imaging-visible Microencapsulated Mesenchymal Stem Cells using XFM Guidance

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Introduction: Stem cell therapy for the heart has shown promise in myocardial repair and prevention of adverse ventricular remodeling after myocardial infarction.¹ Current delivery methods for stem cell transplantation to the heart, which include direct intramyocardial injection and intracoronary infusion, are highly invasive and result in limited retention and viability of implanted cells. The pericardial space, a potential, fluid-filled compartment between the epicardium and pericardial sac, may offer a less invasive approach for localized delivery of stem cell therapeutics to the heart. Although intrapericardial administration of angiogenic growth factors and other cardioactive agents have been successfully performed, the utilization of the pericardial space for stem cell delivery has been rarely explored. The objective of this study was to assess intrapericardial delivery of xenogenic mesenchymal stem cells in imaging-visible microcapsules using x-ray fused with magnetic resonance imaging (XFM) guidance in a swine model.

Materials and Methods: Human mesenchymal stem cell (hMSC) microencapsulation was performed modifying an alginate microencapsulation method² to include 10% (w/v) BaSO₄ (BaCaps). Female Yorkshire pigs (~25 kg, n=7) were randomized to receive either empty BaCaps (~10 ml), naked hMSCs (1×10^8), saline, or Ba-encapsulated hMSCs (8×10^7) via a subxiphoid percutaneous approach. Prior to delivery, ECG-gated cine breath-held short-axis images (TR/TE=25.48/1.59 ms, FOV=280x245 mm, image matrix=192x192, slice thickness=6 mm, flip angle=80°) were acquired on a 1.5 T Siemens Espree scanner to determine ventricular function from endocardial and epicardial borders using vendor software (Argus, Siemens). A navigator-gated 3D whole heart MRI (SSFP, TR/TE=290/1.67 ms, FOV=320x 240 mm, image matrix=256x173, iPAT=2, slice=64, slice thickness=2 mm) was then obtained in diastole to contour ventricular borders for intrapericardial injection. A cardiac-gated c-arm CT (dynaCT, Axiom Artis dFA, Siemens, 190° rotation; 0.5° angle; 20s acquisition; 48 cm FOV) was then obtained. After 3D-3D registration of whole-heart MRI and c-arm CT, a surface rendering of the ventricles from MRI and volume rendered c-arm CT were overlaid on live x-ray fluoroscopic imaging (syngo InSpace 3D/3D Fusion, Siemens) to guide percutaneous access to the pericardial space (Figure 1A). For chronic studies, MRI and c-arm CT imaging were repeated one week after injection. Animals were sacrificed immediately or one week post-delivery for histological analysis.

Results: Ba-encapsulated hMSCs remained highly viable (>95%) post encapsulation. Using XFM, successful intrapericardial access and delivery of BaCaps or Ba-encapsulated hMSCs was achieved in all animals without disrupting coronary vasculature or ventricular puncture. BaCaps were detected on fluoroscopic and c-arm CT images immediately and one week after delivery. Whereas BaCaps were free floating immediately after delivery, at one week the BaCaps had consolidated as a pseudo epicardial tissue patch (Figure 1B). Left ventricular ejection fraction was preserved one week post-delivery (LVEF: $36.8 \pm 4\%$ at baseline vs. $41.5 \pm 5\%$ at one week, n=5, p=NS). Pericardial adhesions and effusion were absent at one week follow up (Figure 1C) with minimal fibrosis demonstrated microscopically. The presence of Ba-encapsulated hMSCs in the pericardial space was easily detected postmortem using HuNA (human nucleic antigen) staining (Figure 1D) while naked hMSCs were seldom retained.

Conclusions: Intrapericardial delivery of Ba-encapsulated hMSCs improves cell retention within the heart. XFM guidance provides a means to increase the safety and reliability of delivery of cellular therapeutics to the pericardial space by taking advantage of both imaging modalities. This approach holds promise in addition for x-ray tracking of allogeneic cellular therapeutics to the heart.

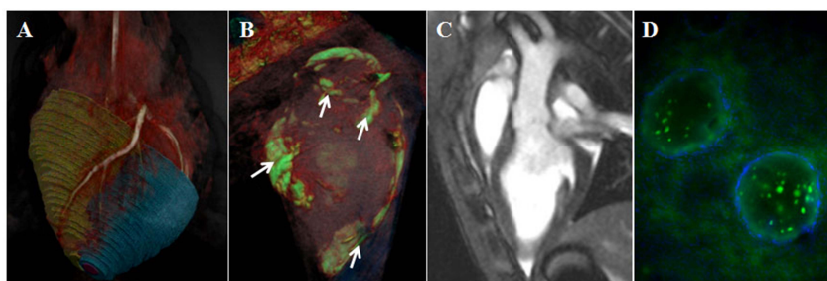


Figure 1: A) XFM of a pig heart showing ventricular boundaries and coronary vasculature. B) C-arm CT image of the heart showing tissue patch-like BaCaps (arrows) on the epicardium one week post-delivery. C) Follow-up MR image of the heart receiving Ba-encapsulated hMSCs demonstrated the lack of pericardial adhesion/effusion. D) HuNA staining showing the presence of Ba-encapsulated hMSCs (green) in the pericardium.

References: 1 Charwat, et al, Thromb Haemost.103(3):564-71 (2010). 2. Lim and Sun, Science, 908-10 (1980)