CARDIAC MAGNETIC RESONANCE TO DETECT CELL DEATH IN VIVO

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Background: Heart failure from myocardial infarction (MI) or doxorubicin (DOX), used in cancer chemotherapy, is preceded by significant cell apoptosis. Real-time, non-invasive detection of early cardiac apoptosis might impact patient treatment and outcomes. Early apoptosis is detected by Annexin V protein (ANX) binding to externalized membrane phosphatidylserine. To this end, we previously conjugated ANX to superparamagnetic iron oxide (ANX-SPIO). This conjugate specifically binds to early apoptotic cardiac cells in culture and is detectable by T2-weighted MRI.

Hypothesis: We tested whether ANX-SPIO could detect cardiac apoptosis, **in vivo**, via T2-weighted MRI (3 Tesla, GE Excite, WI) after ischemic or oxidative injury.

Methods: Mice underwent LAD ligation (MI) or intraperitoneal, cardiotoxic DOX (25mg/kg) injection. After 24-72 hours, ANX-SPIO was given by tail vein, and mice were then imaged in the short- and long-axis cardiac imaging planes by ECG- and respiratory-gated T2-weighted MRI (3 Tesla, GE Excite, Gradient Echo sequence, TR 100ms, TE 20ms, FA 30, FOV 8cm, Matrix 256x256, ST 1.5mm).

Results: After MI (n=3) and DOX (n=2), myocardial T2-MRI signal was detectable within 30 minutes of ANX-SPIO delivery, exhibiting either a focal (MI) or diffuse (DOX) signal distribution (see Fig. 1). There was minimal T2-MRI Peak signal was evident 24 hours after ANX-SPIO delivery, diminishing over 2 weeks. Preliminary cardiac histopathology shows evidence of Prussian Blue iron staining (n=2) in myocardial areas that also displayed MRI T2 signal after doxorubicin exposure and ANX-SPIO delivery. Previous in vitro ANX-SPIO characterization suggested a MRI detection sensitivity between 30-100 labeled myocytes, but in vivo quantification of T2-MRI signal and correlation with cell death is ongoing.

Conclusion: Cardiac MRI using ANX-SPIO can detect areas of myocardial injury in vivo. Distinct MRI signal distributions were noted following ischemic (MI) versus oxidative (DOX) injury. This molecular imaging strategy may help to identify 'at risk' cardiac cell populations.

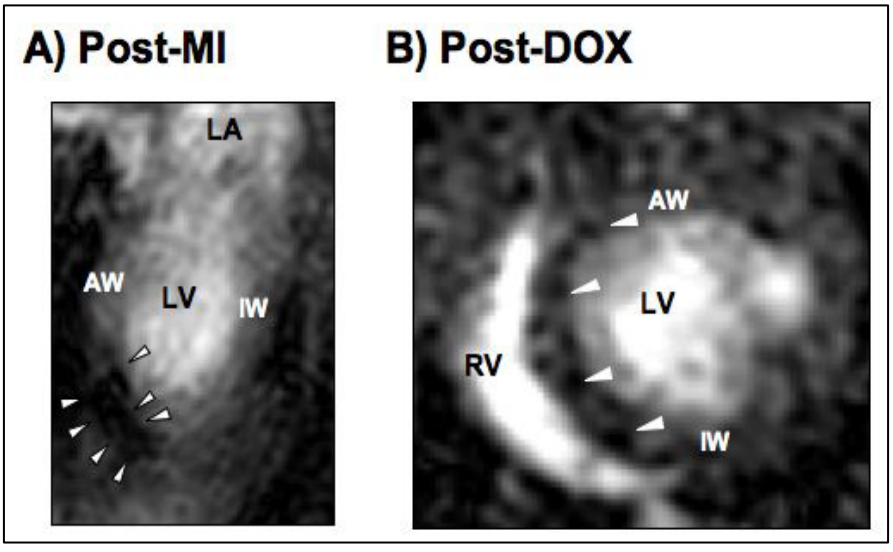

Figure 1: ECG- and respiratory-gated T2-weighted cardiac MRI of mice post-MI (A, 2-chamber view) and post-DOX (B, short axis view), 30 minutes after tail vein injection of 100µl ANX-SPIO. Note *focal* T2 signal void (white arrows) of ANX-SPIO in antero-apex of post-MI heart, and *diffuse* septal, anterior and inferior T2 signal void in post-DOX heart. (LA, left atrium; LV, left ventricle; RV, right ventricle; AW, anterior wall; IW, inferior wall)