Molecular MRI-based Detection of an Alpha-1A Receptor Agonist Treatment for Ischemia-Induced Cardiac Apoptosis

Rajesh Dash[1], Justin Lam[1], Ildiko Toma[1], Yongquan Gong[2], Robert C. Robbins[2], Paul C. Simpson[3,4], and Phillip C. Yang[1]
[1]*Cardiovascular Medicine, Stanford University Medical Center, San Francisco, CA, United States,* [2]*Cardiac Surgery, Stanford University Medical Center,* [3]*Medicine / Cardiology, UCSF Medical Center, San Francisco, CA, United States,* [4]*Cardiology, San Francisco VA Medical Center, San Francisco, CA, United States*

Background:
Myocardial infarction (MI) damages the heart through a combination of programmed cell death (re: apoptosis) and necrotic cell death. The relative contribution of apoptosis to ischemic cardiomyopathy and the benefit of specifically preventing apoptosis post-MI is unknown. Our laboratory previously developed and validated an *in vivo*, MRI-detectable apoptosis probe. Annexin-V (ANX), which binds to cells in the earliest stages of apoptosis, was conjugated to superparamagnetic iron oxide (SPIO) nanoparticles, allowing for the non-invasive detection of early apoptotic cell populations (ANX-SPIO r1: 8.6 ± 0.61 mM^{-1} s^{-1} and r2: 326 ± 16 mM^{-1} s^{-1}). To test the effect of apoptosis reversal in an MI model, we employed A61603 (A6), an α1-adrenergic receptor agonist, which has been shown to rescue cardiac cells from apoptosis through activation of the cardio-protective ERK pathway.

Hypothesis:
A6 therapy will protect against MI-induced cardiomyopathy, and cardiac MRI of systemic ANX-SPIO will detect and monitor this therapeutic effect *in vivo*.

Methods:
Mice underwent MI (via LAD ligation) along with a subcutaneous pump implant that delivered A6 or vehicle (VEH) solution at a rate of 10 ng/kg/day over two weeks. Cardiac MRI (CMR) was performed at 2 days, 1 week, and 2 weeks post MI. ANX-SPIO was injected by tail vein 1 day prior to CMR to assess apoptosis (by T2* signal loss) in parallel with function.

Results:
A6-treated (39±5%, n=3) and VEH-treated (38±10%, n=6) mice exhibited identical ejection fractions (EFs) 2 days post-MI, However, A6-treated mice exhibited significantly ($p<0.05$) higher EFs vs. their VEH-treated counterparts at both 1 week (A6, n=6: 37±9%; VEH, n=5: 18±4%) and 2 weeks (A6, n=5: 33±10%; VEH, n=6: 14±7%) post-MI (Figure 1). Upon T2* decay assessment, A6-treated mice showed significantly ($p<0.05$) less T2* signal loss after ANX-SPIO delivery compared to VEH-treated mice at 1 week post MI (A6 T2*: 19±2ms; VEH T2*: 14±1, n=3), reflecting less myocardial uptake of ANX-SPIO and therefore less cardiac cell apoptosis in A6-treated hearts (Figure 2).

Figure 1.

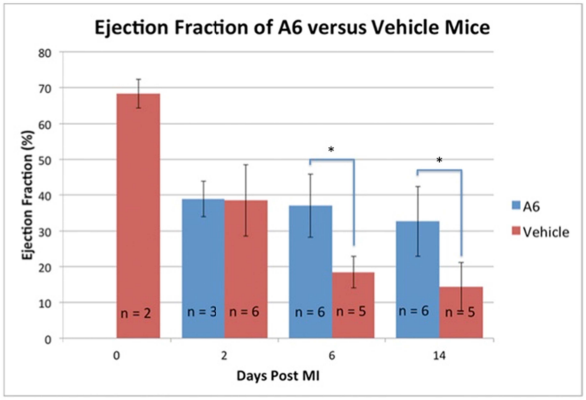
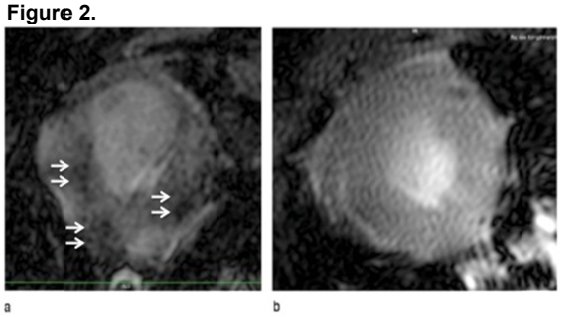


Figure 1: Preserved EF in A6-treated mice at both 1 and 2 weeks post-MI. *$p<0.05$.

Figure 2.



Myocardial T2* Decay from ANX-SPIO: 1 week post-MI

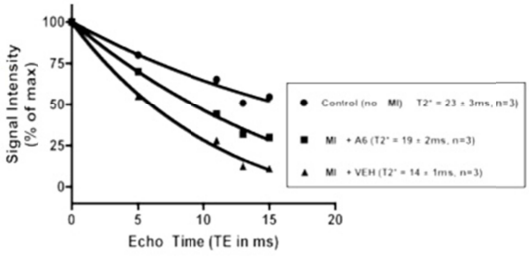


Figure 2: T2* signal loss with increasing iron oxide accumulation in hearts treated with VEH (A, left) versus one treated with A6 (B, right). Patchy T2* signal loss is easily seen is in VEH-treated hearts is (arrows) but not A6-treated hearts. C) T2* signal decay with higher TEs is faster in VEH-treated hearts, with intermediate T2* in A6-treated hearts.

Conclusions:
These results suggest that cardiomyocyte apoptosis is a prominent contributor to the functional impairment of ischemic cardiomyopathy and that A6-mediated cardioprotection from MI-induced apoptosis preserves cardiac function. Moreover, Cardiac MRI and T2* imaging of ANX-SPIO can non-invasively detect A6's therapeutic effect longitudinally.