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Cardiac magnetic resonance detection of dynamic apoptotic signaling in vivo following anti-apoptotic therapy

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Background

Doxorubicin (DOX) is a widely used chemotherapy drug that causes irreversible cardiomyopathy in a growing number of patients. An early detection method for this side effect could positively impact patient care. Previous work validated a molecular MRI probe that linked human Annexin V (ANX), a protein that binds strongly to early apoptotic cells, to superparamagnetic iron oxide (SPIO). T2 weighted (T2W) cardiac MRI of ANX-SPIO was found to detect DOX-induced cardiac apoptosis in mice. Alpha-1AR adrenergic stimulation with A61603 (A6) has been shown to prevent DOX-induced apoptosis and cardiac dysfunction in mice.

Hypothesis

T2-weight (T2W) MRI of an ANX-SPIO molecular probe will detect reductions in DOX-induced apoptosis following cardioprotective A6 therapy.

Methods

FVB/n mice were administered DOX (25 mg/kg, intraperitoneally) plus a subcutaneous mini-osmotic pump secreting saline or A6 (10 ng/kg/day). Fractional shortening was assessed by echocardiography at day 0 and day 6 (Siemens Acuson, Inc.). ANX-SPIO was injected by tail vein 2 days after DOX, and animals were imaged by T2W cardiac MRI 24 hours later (3 Tesla GE Signa Excite T2W GRE sequence: GRE TR 100/TE 10-20 ms/FA 60/FOV 4/matrix 256 × 256/ST 0.8 mm/NEX 6). Ejection fraction was also analyzed by cardiac MRI (Ziosoft, Inc.). Hearts were excised and assayed for Caspase activity (Promega, Inc.) to determine apoptosis signaling.

Results

DOX+A6 mice had preserved fractional shortening (FS %) after 1 week compared to DOX+VEH mice and preliminary T2* decay in mice receiving ANX-SPIO revealed reduced myocardial iron uptake in DOX+A6 vs DOX+VEH (see Figure 1 and Table 1). Preliminary ejection fractions (EF) by cardiac MRI tended to be higher in DOX+A6 mice compared to DOX+VEH.

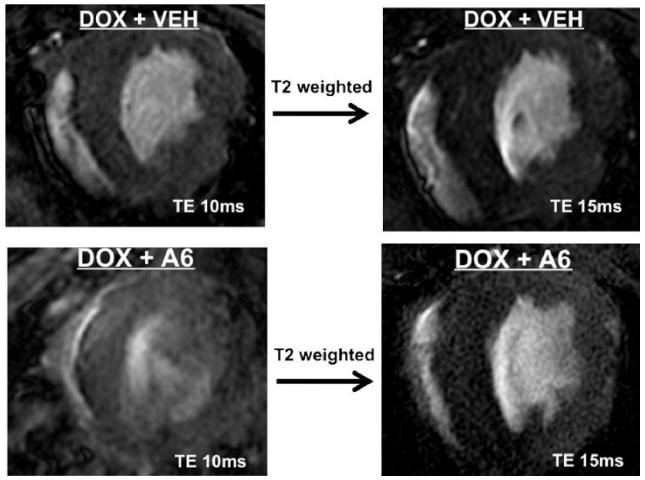

Figure 1
Short-Axis MRI from mice treated with DOX+VEH (top) or DOX+A6 (bottom) and then administered ANX-SPIO by tail vein. Echo time (TE) of 10 ms (left) vs 15 ms (right) is shown. Note rapid T2* signal loss in DOX+VEH hearts, indicating increased ANX-SPIO uptake.

Table 1: Echo, MRI, and Caspase Data

Group	N	FS %	T2* Decay	EF%	Caspase (fold of Control)
Control	3	66 ± 2	29 ± 3 ms	57 ± 8	1.0 ± 0.3
DOX+VEH	3	55 ± 3*	12 ± 2 ms*	27 ± 8*	2.4 ± 0.3*
DOX+A6	2	67 ± 2	22 ± 4 ms	47 ± 2	1.3 ± 0.2

*-p < 0.05 vs control

Decreased uptake of ANX-SPIO into DOX+A6 myocardium was associated with a blunted increase in Caspase 3/7 activation, indicating reduced cardiac apoptosis.

Conclusion

T2W MRI of ANX-SPIO can non-invasively detect cardioprotection by an alpha-1A adrenergic receptor agonist A6 at an early timepoint. MRI of ANX-SPIO may be useful in monitoring apoptotic signaling during therapy for other cardiac disease states.