Early detection of doxorubicin induced diffuse myocardial fibrosis by contrast enhanced magnetic resonance imaging in rabbit modell: compared with histology and electron microscopy.

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Audience: Scientists and medical doctors who are interested in tissue characterization of myocardium and myocardial cardiotoxicity

Purpose: To examine the change of myocardial extracellular volume (ECV) fraction using contrast enhanced magnetic resonance imaging in rabbit during the dilated cardiomyopathy modeling and to investigate the correlation between ECV and the degree of fibrosis and electron microscopic findings in dilated cardiomyopathy rabbit (DCR) models.

Methods: DCR (male adult New Zealand White rabbit, 3–4 kg) models were made by injecting doxorubicin (Doxorubicin Hydrochloride, Cayman) with doses of 1.0mg/kg twice a week for maxi16weeks. Every rabbit underwent cardiac MRI pre- and post- T1 mapping using modified Look-Locker inversion recovery (MOLLI) sequence, LGE, and cine MRI on a clinical 3-T cardiac magnetic resonance (CMR) system before drug administration (Control group) and at 6th , 12th , and 16th week after drug administration (DCR modeling)
On MRI, ECV was calculated at the septum using the myocardial pre, post T1 value, LV blood pool T1 value, and hematocrit(Hct) as follows: ECV = [(1/T1post-contrast myocardium)-(1/T1pre-contrast myocardium)/(1/T1post-contrast blood)-(1/T1pre-contrast blood)] × (1-Hct). Fibrosis was quantitatively measured by image J (V. 1.47, NIH, Bethesda, MA) with digital images of specimens stained with picrosirius red. For electron microscopic findings, specimens were obtained at interventricular septum and lateral wall.

Results and Discussion: Three pre-model and fifteen post-models (five: 6–week, three; 12-week, seven; 16week models) were included. The mean ECV values significantly increased from the 6th week (pre vs. 6th week vs. 12th week vs. 16th week; 29.4±2.0 vs. 31.8±3.4 vs. 36.1±5.4 vs. 40.1±4.1, p-value<0.05).
There was a good correlation between myocardial ECV measured by cardiac MRI and the degree of fibrosis (r=0.75, p-value<0.001). On electron microscopy, myocyte hypertrophy, mitochondrial swelling, pleomorphism and Z band disruption were noted. Collage bundle and strands were significantly increased in extracelluar space in 12 and 16 week model specimens.

Conclusion: The ECV measured by contrast enhanced MRI in DCR models significantly increased from 6th week and ECV showed good correlation with histologic fibrosis.

Reference: 1. Tham, E.B., et al., Diffuse myocardial fibrosis by T1-mapping in children with subclinical anthracycline cardiotoxicity: relationship to exercise capacity, cumulative dose and remodeling. J Cardiovasc Magn Reson, 2013. 15: p. 48

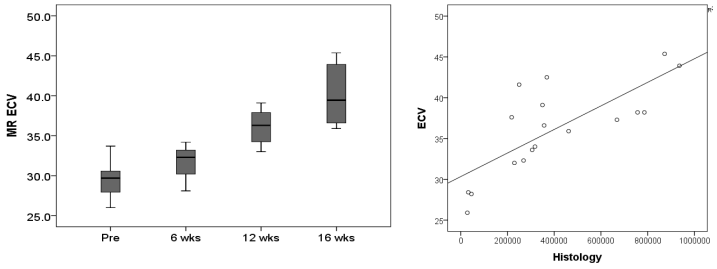

Figure 1. MRI-ECV change according to time elapse after doxorubicin administration (left panel) and correlation with collagen volume fraction on histology (right panel). MRI-ECV increased according to time elapse after doxorubicin administration and well correlated with collagen volume fraction on histology

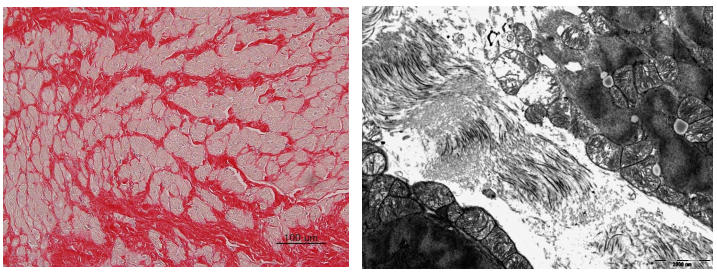

Figure 2. Microscopy with fibrosis stain (left panel) and electron microscopy of fibrosis (right panel) in a rabbit at 16 weeks after doxorubicin administration.