Correlation between cardiovascular T1ρ MRI, histology and future ventricular remodeling in ischemic heart disease.

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Target Audience: The target audience is physicians and scientists interested in imaging biomarkers of cardiovascular disease, especially for the quantitative assessment of ventricular fibrosis in ischemic heart disease.

Introduction: $T_{1\rho}$ MRI has been shown to detect myocardial fibrosis and therefore has great potential to be used as a biomarker for heart disease (1,2). Animal imaging studies revealed that $T_{1\rho}$ relaxation times significantly increased within the first week after infarction, remained elevated during the wound healing process and after complete scar maturation (2,3). These results were found after direct surgical ligation of a major coronary artery or branch. However, most human post-infarction heart disease is a heterogeneous combination of reversibly and irreversibly damaged myocardium, resulting from limited or varying coronary perfusion of the affected artery. Therefore it is not clear whether $T_{1\rho}$ MRI in these animal models truly mimics human injury other than severe coronary artery disease. Our goal was to determine the relationship between $T_{1\rho}$ relaxation times and myocardial pathology at 1 day and 1 and 4 weeks post-infarction in an ischemia-reperfusion animal model. We hypothesized that $T_{1\rho}$ MRI infarct size at 1 day and 1 week is indicative of the time from occlusion to reperfusion and extent of ventricular remodeling at 4 weeks post-infarction.

Methods: Yorkshire swine (n = 10, weight = 45 ± 5 kg) underwent a left thoracotomy and sutures were placed around the circumflex artery proximal to OM1 or OM2 to produce approximately 15-25% left ventricular (LV) infarction area, determined by gross inspection of arterial anatomy. The sutures were released at 45 min (n = 3), 60 min (n = 2) and 90 min (n = 5). At 1 day (n = 3), 1 week (n = 2) and 4 weeks (n = 5) after infarction, serial MRI studies were performed at each time point on a 3 T clinical MRI scanner (Tim Trio, Siemens) with a cardiac array. 3D $T_{1\rho}$-prepared truefisp (TSL = 50 ms, spin lock amplitude = 500 Hz) was performed (resolution = 1.25 x 1.25 x 2 mm) and areas of signal intensity enhancement were indicated. $T_{1\rho}$ relaxation times were measured in a slice containing both infarct and normal myocardial tissue with short axis, 2D $T_{1\rho}$ -prepared truefisp sequence (TSL = 2-50 ms, amplitude = 500 Hz). Other MRI scans performed were retrospective cine truefisp, first pass perfusion and late gadolinium enhanced (LGE) MRI. After sacrifice, the heart was removed, sutures were retied, and gross pathology (TTC) and coronary perfusion anatomy (Evan's blue stain), cell viability (Masson's trichrome stain) and collagen content (Masson's trichrome and picrosirius red) were measured. Statistical analysis was performed by 2-factor ANOVA (factors=occlusion time, post-infarction time) at p<0.05 level of significance.

ischemia \ sacrifice	1 day	1 week	4 weeks
45 min	2		1
60 min			2
90 min	1	2	2

Table 1: # animals /group.

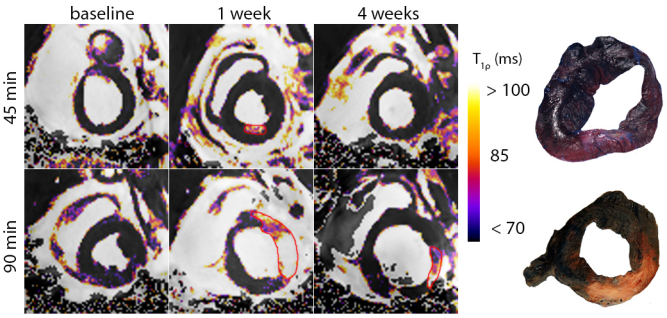

Fig. 1: T1rho relaxation time maps and pathology from two pigs (45 min or 90 min ischemia) at 3 different times (baseline, 1 and 4 weeks post-infarction). The pig with 45 min ischemia had small, subendocardial infarction at 1 week that was not visible on T1rho or LGE MRI at 4 weeks. The pig with 90 min ischemia had a very large infarction at 1 week, which appeared smaller at 4 weeks. Infarction is outlined in red. Absence of blue stain (Evan's) denotes the at-risk area during ischemia. Absence of red stain (TTC) denotes irreversibly injured myocardium.

Results: Ischemia resulted in ST segment elevation during artery occlusion in all animals. There was no visible signal intensity enhancement on $T_{1\rho}$ or T_2 at 1 day post-infarction (p < 0.05) although there was signal enhancement on LGE MRI at the posterolateral wall in all animals, consistent with circumflex coronary occlusion. $T_{1\rho}$ relaxation times significantly increased in this same area at 1 week post-infarction (n = 7, p < 0.01) and the injured area was significantly larger than the LGE enhanced area (n = 7, p < 0.05). The overall size of the injury at 1 week was directly correlated with the time to reperfusion (p < 0.05). At 4 weeks, there remained significant $T_{1\rho}$ relaxation time and LGE enhancement in 4 of 5 animals. Notably, the 1 animal that did not have $T_{1\rho}$ or LGE enhancement at 4 weeks did have a small subendocardial injury at 1 week and microscopic scar at histology (**Fig. 2b**). Both 90 min ischemia animals underwent significant LV remodeling at 4 weeks post-infarction with increased end-diastolic volume. Each of these animals had 90 minute ischemia and large transmural infarctions. Of the remaining 3 animals, the 2 with 60 minute ischemia had smaller, subendocardial infarctions.

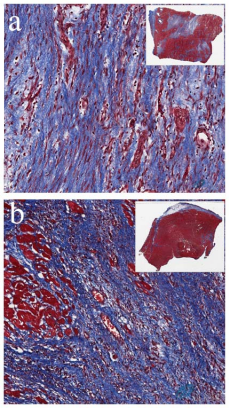

Fig. 2: Trichrome stain of infarcted myocardium. **a,** Segment of infarcted myocardium from an animal with subendocardial infarction 4 weeks after ischemia, depicting deposition of dense collagen fibers. **b,** trichrome stain of infarcted myocardium from 45 min ischemia study in Fig. 1.

Discussion: These results suggest that $T_{1\rho}$ MRI enhancement at 1 week in pigs was indicative of future ventricular remodeling and the duration of ischemic damage. This study provides more evidence that $T_{1\rho}$ detects edema as well as fibrosis, although it is not clear if injury within the first 24 hours is detectable with $T_{1\rho}$. A similar result was found for T_2, which might be expected because the T_2 MLEV-preparation resembles a low power spin lock. A non-contrast $T_{1\rho}$ study in humans post-infarction also found increased signal intensity enhancement early post-infarction (4). Discrimination of edema vs. fibrosis could be potentially determined from $T_{1\rho}$ relaxation times instead of signal enhancement on weighted images. The absence of significant edema on $T_{1\rho}$ or T_2 within 24 hours post-infarction must be further confirmed with histology, but it potentially indicates that there is a mechanism for LGE enhancement after very early acute injury (e.g. permeability of the cell membrane to gadolinium or injury of the coronary vascular network) that is quite different from non-contrast MR methods.

Conclusion: $T_{1\rho}$ can detect myocardial injury to the myocardium in an ischemia-reperfusion animal model at 1 and 4 weeks post-infarction.

References: (1) Witschey, et al. *Magn Reson Med.* 2010;64(5):1453-60. (2) Mustafa, et al. *Magn Reson Med.* 2013;69(5):1389-95. (3) Witschey, et al. J Cardiovasc Magn Reson. 2012:15;14-37. (4) Muthupillai, et al. Radiology 2004;232(2):606-10

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