Rotating Frame, Spin Lattic Relaxation in a Swine Model of Late Ventricular Myocardial Infarction

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Introduction: Following myocardial infarction, structural and biochemical changes occur to the heart muscle, which profoundly affect patient prognosis through the augmentation of wall stress, impaired systolic contractile function and increased probability of aneurism formation. During mid- to late-stages of infarct expansion, progressive thinning and dilatation of the necrotic region results in a decreased volume of myocytes together with compensatory dilatation of the noninfarcted muscle segments. A technique that can, directly or indirectly, monitor scar expansion noninvasively is desirable for the purpose of following animal models of myocardial infarction for use in intervention (1,2), but also for direct visualization of the scar area in patients with ischemic cardiomyopathies. The short T2 transverse relaxation time in the myocardium suggests that there may be strong contributions to the ^{1}H relaxation rate which somewhat obscure endogenous contrast between scar and healthy myocardium (3-5) and we suspect T1ρ imaging can overcome these undesirable effects. Here, we proposed to determine whether T1ρ could distinguish late stage MI and to measure molecular relaxation dispersion in the ischemic and remote regions.

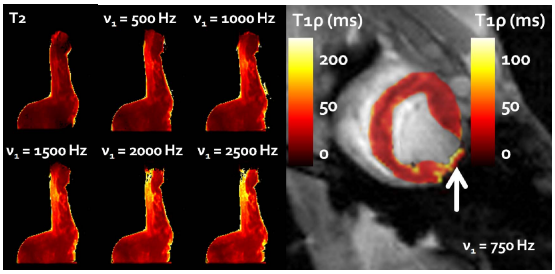

Figure 1: Increasing RF field strength improves scar visualization ex vivo (left, 6 images) and in vivo (B right). Compare T2 (upper left) and T1ρ (ν1 = 2500 Hz, lower right).

Materials and Methods: ***Animal Model and Care*** 5 Yorkshire swine weighing between 20-25 kg were sedated with IM ketamine (25mg/kg), an endotracheal tube was attached and anesthesia induced with isoflurane (1-2%). A left thoracotomy was done during which the pericardial sac was opened and, using a technique developed by our group, the left circumflex artery and mid posterior descending artery were ligated to create a 20-25% area of infarction. After 8 weeks of recovery, the animal was returned to the operating room for a terminal study. A pressure transducer (Millar Instruments, Houston TX) was used for cardiac gating. At the conclusion of the study each animal was euthanized and their heart excised for biochemical analysis. All animals were treated under experimental protocols approved by the University of Pennsylvania's Institutional Animal Care and Use Committee (IACUC). ***In Vivo MRI*** Animals were transported to a 3 T clinical imaging system (Tim Trio Model, Siemens Medical Solutions, Erlangen, Germany). A T1ρ-prepared, centrically segmented, multiecho, gradient echo sequence with Cartesian readout was used to acquire T1ρ-weighted images during systole. The parameters used for acquisition were as follows: bandwidth/pixel = 400 Hz, TR = 3500 ms, TE = 3.3 ms, slice thickness = 8 mm, resolution = 2.34 or 1.56 mm^2, matrix = 128 x 128 or 192 x 192, FOV = 300 mm^2, flip angle = 12 degrees, 12 shots, TSL = 12-48 ms in 5 ms increments, scan time = 4.9 minutes, ν_1 = 750 Hz. ***Ex Vivo MRI*** For each of the 5 animals, the left ventricle was separated from the heart and a section of tissue with approximate dimensions 80 (circumferential) x 20 (radial) x 10 (longitudinal) mm^3 was cut. The tissue was suspended in a custom-built, tissue imaging device containing saline. A T1ρ-prepared fast spin echo sequence was used with the following imaging parameters: bandwidth/pixel = 130 Hz, TR = 3000 ms, $TE_{effective}$ = 15 ms, slice thickness = 1 mm, resolution = 0.23 mm^2, matrix = 256 x 256, FOV = 60 mm^2, echo train length (ETL) = 7, TSL = 10-60 ms in 5 ms increments, scan time = 20 minutes.

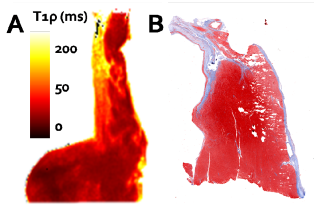

Figure 2: (B) Ex-vivo T1ρ map (ν_1 = 2500 Hz) (C) adjacent a cross-sectional, histological stain for collagen and myocytes. The two sections are not identical, because of normal variations between MR and histological protocols.

Results: *In vivo* relaxation times measured at ν_1 = 750 Hz in the infarct were significantly different (T1ρ = 93.3 ± 12.1 ms), borderzone (T1ρ = 59.6 ± 13.0 ms), and remote myocardium (T1ρ = 49.9 ± 6.1 ms) in 3 animals, an example of which is shown in Figure 1. *Ex vivo* imaging was performed to confirm that the infarct region corresponded anatomically with the infarct scar as it appears by biochemical staining of collagen and cells. There was a near correspondence between prolonged ^{1}H relaxation times (Figure 2A, yellow and bright red color) and the collagenous scar material, which appears as the blue stained tissue in Figure 2B. At TSL times that almost fully relax healthy myocardial tissue, the scar remains moderately unrelaxed on account of its significantly longer relaxation times. The scar extends only partially through the thickness of the myocardial wall, starting at the endocardial side. Ex vivo ^{1}H relaxation times varied with both the applied spin lock amplitude (ν_1 = 0, 500, 1000, 1500, 2000, 2500; $p < 0.05$) and between infarct, borderzone and remote myocardium ($p < 0.05$) (Figure 3). Increasing the amplitude of the spin lock RF field was preferable for scar visualization over T2 in these cases. Between the infarct and remote tissue, ΔT2 was 34.9 ms ± 5.2 ms and increased with spin lock amplitude, such that ΔT1ρ = 74.3 ± 11.3 ms (500 Hz), ΔT1ρ = 99.9 ± 10.8 ms (1000 Hz), ΔT1ρ = 114.0 ± 8.7 ms (1500 Hz), ΔT1ρ = 127.2 ± 15.9 ms (2000 Hz), ΔT1ρ = 137.1 ± 16.1 ms (2500 Hz).

Discussion: T1ρ is shown here to distinguish infarct, borderzone and remote regions of the myocardium. In the acute case, it was suggested that following myocardial apoptosis and cell death, there is a leakage of protein material from the sarcolemma into the extracellular space, minimizing the effect of proteins on water molecules (6,7). Preliminary data (collected, but not shown) suggests that a significant dispersion is observed in the acute case, such that conventional methods of infarct visualization by delayed Gadolinium techniques could be circumvented by endogenous contrast by T1ρ. An investigation of ^{1}H relaxation dispersion suggested that all three curves in Figure 3 could be modeled with a single correlation time, although likely dispersion is some combination of coupling between water ^{1}Hs modulated by slow tumbling of proteins molecules, multiple sites of chemical exchange, as well as direct magnetization transfer effects. By increasing the spin lock amplitude, one can maximize the relaxation time differences between infarct and remote myocardium, however, one also can overcome the significant B0 homogeneity in the cardiothoracic cavity. The air-filled lung together with cardiac and respiratory motion can have a considerable, deleterious effect on B0 field homogeneity in the chest. This problem was compounded in the present situation through the use of a left ventricular, metallic, pressure transducer used for pacing the swine.

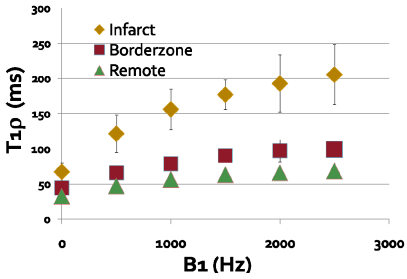

Figure 3: T1rho relaxation dispersion in infarct, borderzone and remote regions in 5 animals.

Conclusion: T1ρ imaging was used to noninvasively quantify MI scar, borderzone and remote myocardium. This technique has immediate application to the assessment of new cardiac interventions and imaging of scar formation in patients with MI. These techniques may be particularly beneficial for patients with kidney disease or who cannot otherwise have a gadolinium-based delayed enhanced MRI scan.

References: (1) Pilla, et al. *Circulation*. (2001) (2) Blom, et al. *Ann. Thorac. Surg.* (2007) (3) Simonetti, et al. *ISMRM Radiol.* (4) Abdel-Aty, et al. *Circulation* (2004). (5) Cobb, et al. *JMRI.* (2009). (6) Huber, et al. *JMRI* (2006). (7) Muthupillai, et al. *Radiology*. (2004). **Acknowledgements:** This work was supported by Award P41RR002305 from the National Center for Research Resources. We also thank Niels Oesingmann of Siemens Medical Solutions for his assistance.