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MYOCARDIAL ISCHEMIA AND INFARCTION

T2 Fluctuations in Ischemic and Post-Ischemic Viable Porcine Myocardium in Vivo

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ABSTRACT

T2 relaxation can augment delayed-enhancement viability imaging because it is sensitive to tissue edema and microcirculatory oxygen state. We demonstrate the T2 'signatures' of sub-lethal ischemia and stunning in porcine myocardium perfused by the distal left anterior descending artery, by imaging during percutaneous balloon occlusion for 25 minutes and subsequent reperfusion ($n = 9$). Muscle displayed ischemic dysfunction and partial post-ischemic functional recovery ($p \leq 0.0004$), concommitant with an elevated post-ischemic T2 ($\Delta T2 = 27 \pm 18\%$, $p = 0.005$). TTC staining verified muscle viability. The T2 fluctuations may reflect hyperemia and tissue cellular edema in accord with the known pathophysiology of ischemic and post-ischemic yet viable muscle.

INTRODUCTION

There is a need for development of non-invasive imaging endpoint measurements which can differentiate between states of myocardial dysfunction. These measurements can then augment blood markers and survival data in pre-clinical and clinical trials of pharmacological and mechanical interventions (1–3).

An effective tissue characterization is achievable using a combination of viability, metabolism, function, and perfusion-weighted measurements, especially so if the imaging information is quantitative and if the endocardium and epicardium are distinctly resolved. These factors suggest a clinical evaluation centred on magnetic resonance imaging, stress echocardiography, and positron emission tomography as core technologies (4, 5).

An on-going diagnostic challenge is the differentiation between stunning and acute and chronic infarct. Friedrich demonstrated clinically that an important role may exist for T2-weighted imaging in differentiating acutely from chronically infarcted muscle (6). However, both delayed enhancement and T2-weighted imaging were not effective for tissue categorization at very early stages of injury. Others have shown that, in sublethal ischemia and reperfusion, post-occlusive hyperemia persists for as long as 15 minutes and a slight edema persists for at least 1 hour but not 24 hours (7, 8). This paper reports our observations of fluctuations in quantitative myocardial T2 relaxation in a porcine model of sub-lethal ischemia and the very early stages of reperfusion. Since T2 increases with hyperemia and edema, we expect to see a T2 elevation immediately after reperfusion which gradually diminishes with time.

Keywords: Myocardial Stunning, Myocardial Viability, T2 Relaxation, Magnetic Resonance Imaging
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METHODS

Studies were conducted in Yorkshire pigs (22–28 kg) (Riemen's Fur Ranch, St. Agatha, Ontario) using procedures and protocols approved by the Animal Care Committee of Sunnybrook and Women's College Health Sciences Centre.

Animal pre-medication

Premedication consisted of a ketamine/atropine cocktail (35 mg/kg ketamine hydrochloride and 0.05 mg/kg atropine) and masking at 5% halothane in oxygen. Anesthesia was maintained using 2% isofluorane. Animals received pre-operative intravenous bolus followed by constant infusion of both amiodarone (75 mg bolus, 1.5 mg/kg/hour infusion) and lidocaine

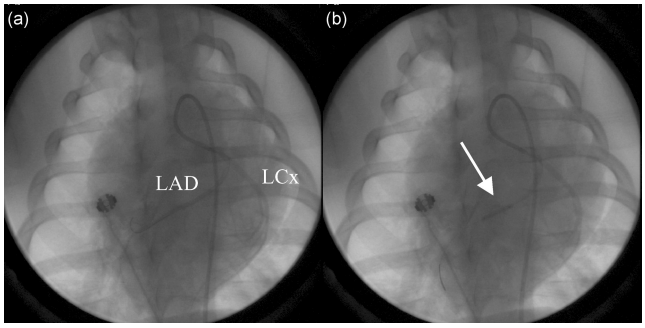

Figure 1. Fluoroscopic demonstration of balloon deployment. (a) The unobstructed coronary arterial distribution of iodinated contrast into the left anterior descending artery (LAD) and circumflex artery (LCx). (b) Via femoral access, a balloon (depicted by the white arrow) is positioned and inflated using iodinated contrast, at a location distal to the second septal branch of the left anterior descending coronary artery (LAD). The distribution of iodinated contrast distal to the inflated balloon is negligible in the LAD but preserved in the LCx.

(20 mg bolus, 3 mg/kg/hour infusion). Animals also received metropolol during the 5-day interval prior to experimentation (50 mg/day, in feed).

Surgical preparation

All surgical intervention and scanning was performed with the animal oriented supine in a plexiglass case. Percutaneous placement of instrumentation was guided by x-ray fluoroscopy (OEC 9800 GE Healthcare, Waukesha, WI), for which the animal's plexiform case is radiolucent. A 3-mm balloon catheter (Boston Scientific, Natick, MA) was placed distal to the second diagonal branch of the left anterior descending artery (LAD) via femoral access. Transient balloon inflation to 8 atmospheres during iodinated contrast injection verified the absence of residual flow to the anterior and septal regions of the apical myocardium (Figure 1a and b).

MRI scanning

All imaging was performed on a 1.5 Tesla GE Signa (GE Medical Systems, Waukesha, WI). A 5-inch surface coil on the animal's chest provided signal reception. The plethysmograph trace received from the pig's tail through the peripheral leads of either the GE Signa or a physiological monitoring system (In Vivo Research, Orlando, FL) provided a signal for cardiac gating. The forelimbs were secured to the base of the plexiform to reduce respiratory artifacts.

A total of 9 animals were subjected to repetitive acquisition of functional and T2 data in two 5-mm apical short-axis slices and in up to four states; baseline, during complete coronary occlusion of 25 minute duration, and at 5 and 30-minutes post balloon deflation. Additional measurements were performed in two animals at later time points of 90 and 150 minutes. Cardiac functional data was acquired using a steady-state free precession (SSFP) sequence (45° flip angle, 125 kHz bandwidth, 4 NEX, 256 × 128, 24 cm FOV). T2 fluctuations were monitored using a cardiac-gated magnetization-prepared spiral imaging sequence (1.38 mm in-plane resolution, 24 cm FOV 6 ms refocusing, 2 echo times of 11 and 55 ms, 6 NEX, cardiac gating to late systole and across 3 or 4 cardiac intervals). The short-axis imaging slices were positioned 15 and 20 mm from the apex and apical to the severe susceptibility artifacts of the instrumentation (Fig. 2a) (9).

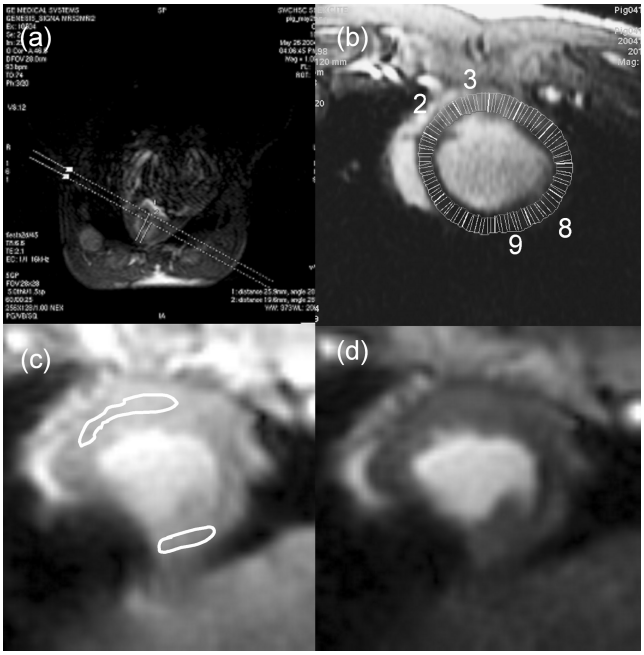

Figure 2. MRI Methodology. (a) prescription of two 5 mm imaging slices apical to the artifacts from instrumentation and about 15 to 25 mm basal of the apex. (b) definition of twelve segments for functional assessment. Segments 2 and 3 provide the dysfunctional region and segments 8 and 9 provide the control region. The bottom row displays T2-weighted images with representative anterior and posterior regions-of-interest at echo times of (c) 11 ms and (d) 55 ms.

Hearts from four animals were excised post-mortem for staining in triphenyltetrazolium chloride (TTC). Four hours of reperfusion were allotted prior to their sacrifice to flush TTC-binding-enzymes from any regions of infarction.

MRI data analysis

Functional analysis used 100 equidistant chords which were placed perpendicular to the center-line between motion-corrected manually-drawn diastolic and systolic endocardial boundaries, termed the center-line method (Mass plus software 5.1, MEDIS, Leiden, Netherlands) (10). Chords were divided into 12 segments. The average of two antero-septal segments (#2 and #3) provided the dysfunctional region while the average of two remote postero-lateral segments (#8 and #9) provided the control region (Fig. 2(b)). The per segment systolic wall thickening (%SWT) was calculated as the average per chord systolic

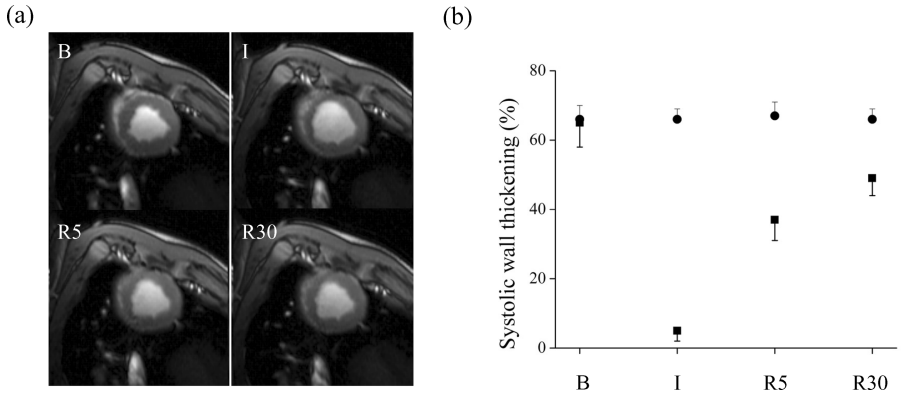

Figure 3. Systolic wall thickening results. (a) representative SSFP images at a peak systolic phase at baseline (b), 5 minutes of ischemia (I), 5 minutes of reperfusion (R5), and 30 minutes of reperfusion (R30); and (b) time courses of systolic wall thickening in anterior (squares) and control (circles) segments. The error bars depict 1 standard deviation.

wall thickness, according to Equation 1:

$$\%\mathrm{SWT} = 1/\mathrm{N} * \sum(\mathrm{SWT} - \mathrm{DWT})/\mathrm{DWT} * 100 \qquad [1]$$

where N is the per region chord number, $\sum$ indicates a summation over per region chords, SWT is the systolic wall thickness (mm), and DWT is the diastolic wall thickness (mm).

T2 analysis used antero-septal and remote postero-lateral regions-of-interest (ROIs), encompassing 15 to 30 volume elements (about 0.15 to 0.3 cm^3) and drawn manually at locations judged to be insensitive to biases from partial voluming and magnetic susceptibility variations (Fig. 2c and d) (11). The signal reduction between the echo times was fitted to a mono-exponential decay using custom software (xcinema, Stanford University, Palo Alto, CA). T2 values were in concordance with a second reviewer. Statistical significance in parameter changes was evaluated on a per animal basis by applying Student's paired *t*-test to the averages of parameter values in the MRI slice pair.

RESULTS

Representative images and the time courses of systolic wall thickening and T2 are displayed in Figs. 3 and 4. The preservation of viability of myocytes in dysfunctional muscle was verified in four animals by the uniformity of brick-red TTC staining.

Anterior myocardium

Antero-septal muscle displayed significant functional depression from baseline at all experimental time points (during ischemia: $\Delta\mathrm{SWT} = -45 \pm 10\%$, $p < 0.0001$, $n = 8$; at 5 minutes of reperfusion, $\Delta\mathrm{SWT} = -30 \pm 9\%$, $p < 0.0001$, $n = 8$; at 30 of minutes reperfusion, $\Delta\mathrm{SWT} = -19 \pm 9\%$, $p = 0.0002$, $n = 9$). The post-ischemic muscle demonstrated a very early and significant functional recovery from ischemic values (at 5 minutes of reperfusion, $\Delta\mathrm{SWT} = 15 \pm 7\%$, $p = 0.0004$, $n = 8$; at 30 minutes reperfusion, $\Delta\mathrm{SWT} = 27 \pm 14\%$, $p = 0.05$, $n = 8$). The improvement in function of post-ischemic muscle continued between five and thirty minutes of reperfusion ($\Delta\mathrm{SWT} = 12 \pm 12$, $p = 0.02$, $n = 8$).

Concurrent with post-ischemic functional recovery was a significant elevation in antero-septal T2 relaxation from baseline which was sustained through the first thirty minutes of reperfusion (at 10 minutes of ischemia: $\Delta\mathrm{T2} = 8 \pm 11\%$; $p = 0.07$, $n = 8$; at 20 minutes of ischemia: $\Delta\mathrm{T2} = 13 \pm 18\%$, $p = 0.09$, $n = 7$; at 5 minutes of reperfusion: $\Delta\mathrm{T2} = 27 \pm 18\%$, $p = 0.005$, $n = 8$; and at 30 minutes of reperfusion: $\Delta\mathrm{T2} = 22 \pm 22\%$, $p = 0.03$, $n = 8$). The elevation in post-occlusion T2 from ischemic values

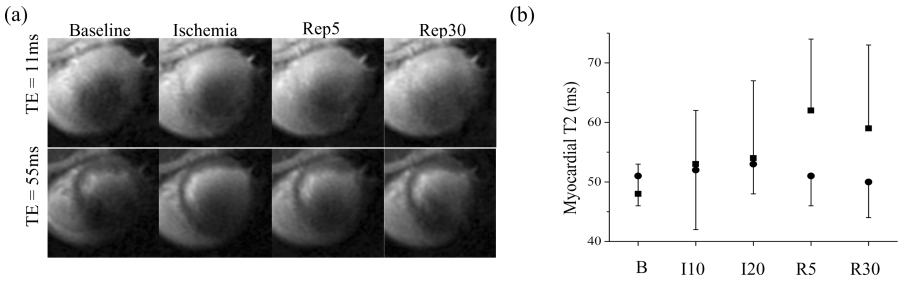

Figure 4. T2 results. (a) representative T2-weighted images at baseline, ischemia, and post-ischemia time-points; and (b) time courses of T2 in antero-septal (squares) and postero-lateral control (circles) ROIs. The error bars depict one standard deviation.

also reached a high level of significance ($p < 0.01$). T2 relaxation tended to return to baseline at later time points post-reperfusion (2 animals evaluated at 90 and 150 minutes post-reperfusion, data not shown).

Control myocardium

Neither fluctuations from baseline in SWT or T2 were significant in remote muscle at all experimental time-points.

DISCUSSION

We have developed and validated a porcine model of sublethal ischemic and post-ischemic viable myocardium by percutaneous balloon inflation distal to the second diagonal branch of the left anterior descending coronary artery. T2 fluctuations from baseline were evaluated in dysfunctional and control segments at time points during ischemia and the very early stages of reperfusion and demonstrated to elevate significantly in post-ischemic muscle displaying functional recovery. A subset of the telling phenotypic characteristics of stunning were demonstrated including reversible contractile dysfunction via SSFP and myocardial viability via TTC staining post-mortem (12). The porcine stunning model characteristics are consistent with the canine stunning model of Kraitchman, whom demonstrated an alleviation of contractile dysfunction within 30 minutes of short-term coronary occlusion and the canine stunning model of Thornhill, whom demonstrated a preserved Gd-DTPA partition coefficient at 3 weeks of reperfusion (13, 14).

MRI T2 relaxation in the very early stages of ischemia and reperfusion injury has not previously been considered in a sublethal injury model. Slutsky et al demonstrated small but marked T2 elevations from control in ischemic canine myocardium ex vivo (15). Higgins et al demonstrated T2 elevations of near 10% in canine myocardium subjected to a three hour coronary occlusion (16). Wisenberg et al demonstrated more dramatic early T2 elevations in canine infarct, 25% in unreperfused infarct and 60% in reperfused infarct (17). The fluctuations did not suffice for robust early infarct detection in patients subjected to septal artery embolization (18).

Contractile function and stunning

The existence of both an early but incomplete recovery of contractile function and a slow return to normal function is consistent with the current understanding of stunning (19). Ischemic muscle is known to deplete rapidly its chemical energy stores to the extent that ATP mass is reduced to 63% of normal and total adenosine nucleotide mass is reduced to 50% of normal at 15 minutes of ischemia in canine myocardium (20). Reperfusion restores rapidly the ATP charge (and thus activities of ATPases) though restoration of adenosine nucleotide mass occurs on the time scale of days (21). The slow return to normal function is also concurrent with the replacement of cellular components which were post-translationally modified by oxidative stress very early in reperfusion, including the troponins (22, 23).

Correlates of T2 relaxation and stunning

Both of hyperemia and total water content are accepted correlates of myocardial T2 relaxation which are perturbed at very early time points in post-ischemic yet viable myocardium. The early accumulation of lipid in ischemic and stunned myocytes also elevates T2 relaxation but this effect is not measured with our fat-suppressed methodology (24, 25).

From myocardial vasodilation studies of the past decade, the T2 elevation from baseline is on the order of 15% when flow and perfusion reserves are normal (9). Jennings et al demonstrated that the hyperemia of canine myocardium is sustained for close to 15 minutes following a 15 minute complete coronary occlusion (7), while Franco-Cereceda demonstrated a 5-fold elevation in coronary blood flow subsequent to a 5 minute ischemia in porcine heart muscle (26).

An elevation in total water content of near 3% is a hallmark of unreperfused acute infarct and a contributor to its T2 elevation of up to 25% from control (16, 17, 27). In stunning, each of Jennings and Reimer have demonstrated an elevated total tissue water content, which was sustained for up to 24 hours (8, 28). At least the first hour of this mild edema is concurrent with slight but significant elevations in tissue sodium and potassium. Jennings and Reimer have also demonstrated a slight but progressive tissue edema during prolonged ischemia, which is synchronous with a progressive myocyte influx of sodium and efflux of potassium (28).

Correlates of T2 and early ischemia

The rapid depletion of high energy phosphate bonds in ischemic myocytes, and more gradual transformation of adenosine triphosphate to by-products including adenosine and inosine, is indicative of highly deoxygenated hemoglobin. A reduction in myocardial T2 relaxation by an elevated hemoglobin paramagnetism was not observed by us, possibly because of the near-total desaturation of hemoglobin in the normal coronary circulation as well as a countering and early elevation in total tissue water of near 5% mediated by glycogen utilization with subsequent cellular vacuolization and lactate accumulation (21, 28).

Clinical Implications

Cardiac MRI is already a validated method for assessing myocardial viability using delayed hyperenhancement (DHE), coronary perfusion and contractile reserve (5, 29). T2-weighted imaging, which highlights edematous tissue, has been used in association with DHE to differentiate acute from chronic infarction (6). This current study could add important information to frequently encountered clinical scenarios, particularly when there is clinical evidence of an acute coronary syndrome but no evidence of infarction. In the acute setting, near-normal or slightly elevated T2 relaxation in association with regional contractile dysfunction, but no DHE, may signify viable myocardium. Further evaluation of T2 fluctuations in unreperfused and reperfused infarction models may clarify the methodology's

utility in identifying the presence and extent of peri-infarct ischemia.

Experimental limitations

T2 measurement methodology

Parameter optimization for feasibility in robust myocardial T2 relaxation evaluation in vivo is discussed in detail by Foltz et al (11). This optimization minimizes spiral blurring of myocardial and chamber blood signals within SNR and imaging time constraints in a two echo time acquisition; a design which trade-offs rigor in relaxation modeling for accuracy and precision in the measured T2-weighted signal intensities within clinically-feasible scan times. Note that the imaging optimization does not account consistently for spiral imaging artifacts local to the heart/lung interface and the coronary veins, which are more severe in pigs than humans (11, 30).

A two echo time fitting provides only an approximation of the true relaxation complexity of muscle (31). However, the extension to fitting of even the next most simple relaxation model, that of water exchange between intravascular and extravascular tissue compartments, would require upwards of a 16-fold increase in imaging time at constant spatial resolution (ie, 45 minute scan times at 4 echo train durations of 0, 24, 48, 96 ms) (32). A two echo time fitting is also prone to noise variability. However, we reduce T2 noise variability to within 1% by achieving an antero-septal per voxel SNR of 110 ± 24 at an echo time of 11ms and by separating echo times by approximately 1.1*TE, which maximizes precision in a 2-echo time fit (33). Noise bias, which is the baseline remote from tissue in magnitude images, is minimized by maintaining an antero-septal per voxel SNR of 10 or more at an echo time of 55ms.

Anaesthesia and cardioprotection

Common to modern anesthesia is dose-dependent cardioprotection. Isofluorane actions at experimental concentrations between 1 and 3% include a direct anti-inflammatory effect on leukocytes, in addition to myocardial pre-conditioning and potent but partial vasodilation of the coronary vasculature (34, 37). An enhancement of post-ischemic T2 fluctuations under maintenance with the more weakly cardioprotective halothane would implicate indirectly an underlying hyperemia and its mediation by an accumulation of adenosine.

CONCLUSIONS

We have developed and validated a porcine model of sublethal ischemia and stunning, via percutaneous balloon occlusion of the left anterior descending artery. Several tissue characteristics were demonstrated, including reversible contractile dysfunction via SSFP and myocardial viability via TTC staining post-mortem. The significant T2 fluctuations during very early reperfusion may reflect hyperemia and tissue cellular edema in accord with the known pathophysiology of ischemic and post-ischemic yet viable muscle.

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