Myocardial R2 and R2* vary linearly with cardiac iron in human heart

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Introduction: Iron-induced cardiac dysfunction is a leading cause of death in transfusion dependent anemia [1]. MRI relaxivity parameters, R2 (1/T2) and R2* (1/T2*) have been previously shown to be accurate non-invasive predictors of liver iron stores [2]. Low cardiac T2* is associated with poor cardiac function in iron-overloaded patients, suggesting that MRI may predict cardiac iron as well [3]. However, because of the invasive nature of myocardial biopsy and the large variability in myocardial iron distribution [4], no similar relationship has been demonstrated between myocardial iron and MRI relaxation parameters. R2 and R2* techniques have relative advantages and disadvantages with respect to iron-sensitivity, motion artifacts and susceptibility artifacts. The purpose of this study was to systematically examine the relationship between R2, R2* and cardiac iron in sections of a freshly deceased heart from an iron loaded patient.

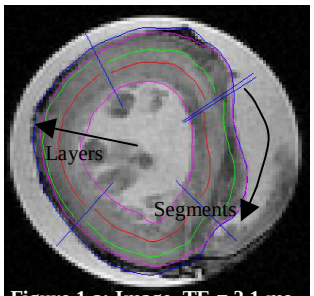

Figure 1 a: Image, TE = 2.1 ms

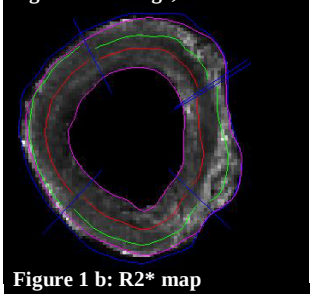
Figure 1 b: R2* map

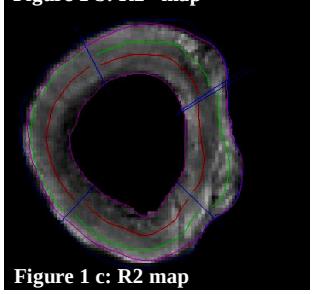
Figure 1 c: R2 map

Methods: We studied one thalassemia major patient with longstanding cardiac and liver iron overload who succumbed to overwhelming sepsis. Informed consent for MRI and limited heart autopsy was obtained from the patient's family, based on a protocol approved by the Childrens Hospital Los Angeles Committee on Clinical Investigations. The patient underwent an in-situ MRI (1.5 T GE CVi, 4-element torso coil) within 3 hrs. of demise, with an assessment of cardiac T2 (single-echo, TE = 9, 11, 15, 20, 30, 40, 60, 100 ms, TR = 1 s) and T2* (multi-echo gradient echo, TE = 2.1, 4.8, 7.5, 10.2, 13.0, 15.7, 18.4, 21.1 ms, TR = 1 s) along the short axis. The heart was harvested 12 hrs. later, sectioned and maintained under moist conditions at room temperature. Similar in-vitro MRI (using knee coil) was performed on 3 slices 12 hrs. later. Each of these slices were sectioned into 12 sub-divisions (4 circumferential segments, each divided into 3 radial layers: endocardium, myocardium and epicardium) and sent to Mayo Medical Laboratory (Rochester, MN) for iron quantitation. The TE-dependent images were fit to monoexponential function with a variable offset on a pixel-wise basis.

Results: In-situ mean R2* value (after demise) for entire myocardium of a mid-papillary slice was 327 ± 40 s^{-1}; this value was 5% lower from previous in-vivo R2* (a year before demise), consistent with patient's transfusion and chelation history. Figure 1 a, b, c show anatomical, R2* and R2 images respectively of a representative in-vitro slice (12 sub-divisions, approximately the same as sectioned biopsies, are indicated). Note the bright epicardium (high relaxivity) in both R2 and R2* maps, consistent with previous autopsy reports [4]. R2 and R2* demonstrated matching regional variations in both in-situ and in-vitro images. Relaxivity histograms had similar shapes in-situ and in-vitro but mean values were 30% lower for the in-vitro measurements. Slice wet-to-dry weight ratio was 6.87±0.31, suggesting that increased intracellular water post-mortem accounted for the difference. R2 and R2* rose linearly with cardiac iron for all 3 extracted myocardial slices (in-vitro), with an r^2 of 0.57 and 0.46 respectively, $p < 0.001$ (Figure 2). R2* and R2 also varied linearly with one another, r^2=0.69 (Figure 3).

Discussion: R2 and R2* both increase proportionally to iron in liver [2], but there is disagreement whether these parameters reflect iron stores in the heart. This paper clearly demonstrates concordance of R2 and R2* measurements with one another and with cardiac iron. These data, combined with with R2 and R2* measurements from normal patients, will even provide crude calibration curves for cardiac R2 and R2* measurements. In in-vitro measurements, R2 measurements had superior homogeneity and concordance with iron levels than R2* measurements. R2* measurements demonstrated circumferential variability that was independent of iron content, likely representing extrinsic susceptibility artifacts. However, R2-R2* concordance was relatively high in the interventricular septum, the region typically used for in-vivo measurements. In practice, R2* measurements may be preferable in-vivo because they can be acquired in a single breath-hold and are relatively robust to cardiac motion during contraction. R2 measurements require long echo times, relative to cardiac contraction intervals, leading to signal loss from inadequate spin refocusing. In summary, cardiac MRI can be used to estimate cardiac iron content in transfusional overload. R2 and R2* changes are tightly correlated with one another, suggesting that either technique or their surrogates (signal intensity ratios) can be used clinically.

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References:

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Figure 2

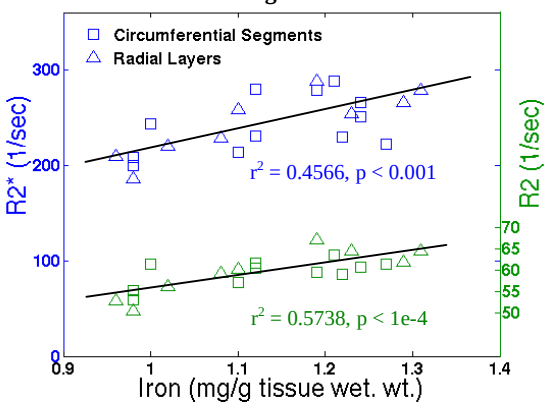

Figure 3