Ann & Robert H. Lurie Children's Hospital of Chicago

MR Imaging of Cardiac and Liver Iron Overload

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Ann & Robert H. Lurie Children's Hospital of Chicago

No financial disclosures

Lurie Children's Master MRI Research Agreement with Siemens Healthcare

MRI Assessment of Iron Overload

- Iron overload states
- Index iron overload case
- Iron imaging techniques
- MR iron imaging program

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Iron Overload States

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Iron overload states

- β–thalassemia
- Sickle cell disease
- Hemochromatosis
- Blackfan-Diamond
- Dyserythropoetic anemia
- Congenital sideroblastic anemia
- Myelodysplastic syndromes
- Transfusional related

β–thalassemia major

- Profound anemia due to absence or severe reduction of the beta globin chains of adult hemoglobin
- Requires transfusions from infancy to maintain adequate hemoglobin
- Transfusional siderosis
- Increased intestinal absorption of iron
- Iron accumulation in organs
  - Liver, heart
  - Bone marrow, spleen, endocrine organs, lymph nodes
- Chelation therapy to remove excess iron

Wood JC, et al. Ann N Y Acad Sci. 2005; 1054: 386-395
Argyropoulou M. Pediatr Radiol 2007; 37: 1191-1200

Sickle cell disease

- Red cell transfusions highly effective to treat/prevent severe complications
  - Anemia symptoms, stroke, acute chest, splenic sequestration
  - Chelation therapy
  - Erythrocytapheresis (red cell exchange) to control iron load
- Iron accumulation in liver
- Lower presence of cardiac siderosis
- Kidney cortex iron due to intravascular hemolysis
  - Not due to transfusional iron load
  - No medullary accumulation
  - No correlation with liver iron

Drasar E. etal. (2012) Br Jour of Haematology, 157, 645-647.
El Beshlawy (2014). Ann of Hematology, **93,** 375-379.
Schein A. Annals of Hematology, **93,** 375-379.
Wood. (2008). Blood Reviews. Suppl 2 S22-S41.

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Iron overload states

- β-thalassemia major
  - Require transfusion from birth
- Generally no cardiac iron loading until 2nd decade
  - Adequately chlelated
  - Exposure to minimum of 70 units of blood

- Sickle cell disease
  - Transfusions begin later in life
  - 20% transfused to avoid stroke, bone infarcts, acute chest
- Cardiac dysfunction occurs in SCD
  - Cardiac iron loading rare

Wood J. Blood Reviews (2008) 22 Suppl. 2, S14–S21

Iron overload states

- Liver biopsy and serum ferritin have been surrogates for evaluating total body iron load
- Cardiac iron does not directly correlate with serum ferritin or liver iron concentration
- Death from iron overload cardiomyopathy was leading cause of death in β-thalassemia major
  - Now rare in centers with MRI screening

Anderson LJ, et al. Eur Heart J 2001; 22:2171-2179.

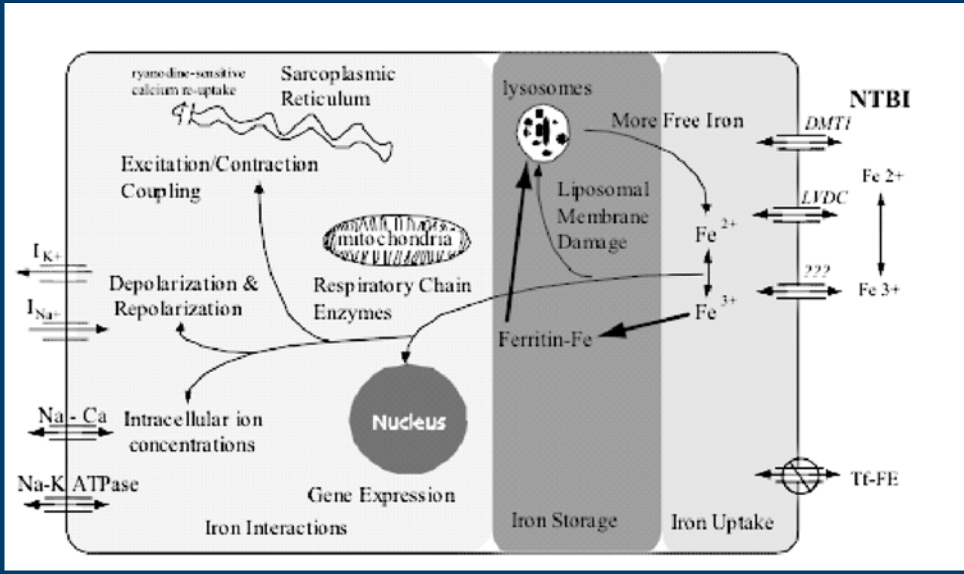
Wood JC, et al. Blood 2005; 106:1460-1465.

Wood JC. Circulation 2005; 112:535-543.

Wood J. ASH Education Book December 10, 2011 vol. 2011 no. 1 443-450

Iron overload states

- Risk of death from cardiac iron varies by disease, transfusional burden, chlelation
- Toxicity is due to non-transferrin bound iron (NTBI)
  - Iron is normally transferrin bound
  - Increased iron exhausts transferrin and leads to NTBI
- Redox cell damage
  - Conduction disturbances
  - Decreased systolic function
- Systolic dysfunction late marker
  - Heart failure unpredictable/rapid



Anderson LJ, et al. Eur Heart J 2001; 22:2171-2179.
Wood, JC. Blood Reviews. 2008:22 S14-S21.
Wood JC et al. Ann N Y Acad Sci. 2005; 1054: 386-395.

MRI assessment of iron overload

- Cardiac biopsy
  - Invasive and limited by sample size and location
- T2* imaging used to non-invasively quantify heart and liver iron
  - Only images stored iron, not NTBI
- Cardiac and liver T2* values correlate with heart and liver iron load

Wood JC et al. Ann N Y Acad Sci. 2005; 1054: 386-395.
Wood JC et al. Circulation 2005; 112:535-543.

MRI assessment of iron overload

- Siderotic cardiomyopathy is reversible
  - Improvement in systolic function first
  - T2* improvement later (5.7-7.9 ms/year)
  - Decrease in heart iron takes longer than decrease in liver iron

Anderson L. Br J Haematol 2004; 127:348 - 355.

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Index case

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22 yo β-thalassemia major
Routine T2* evaluation

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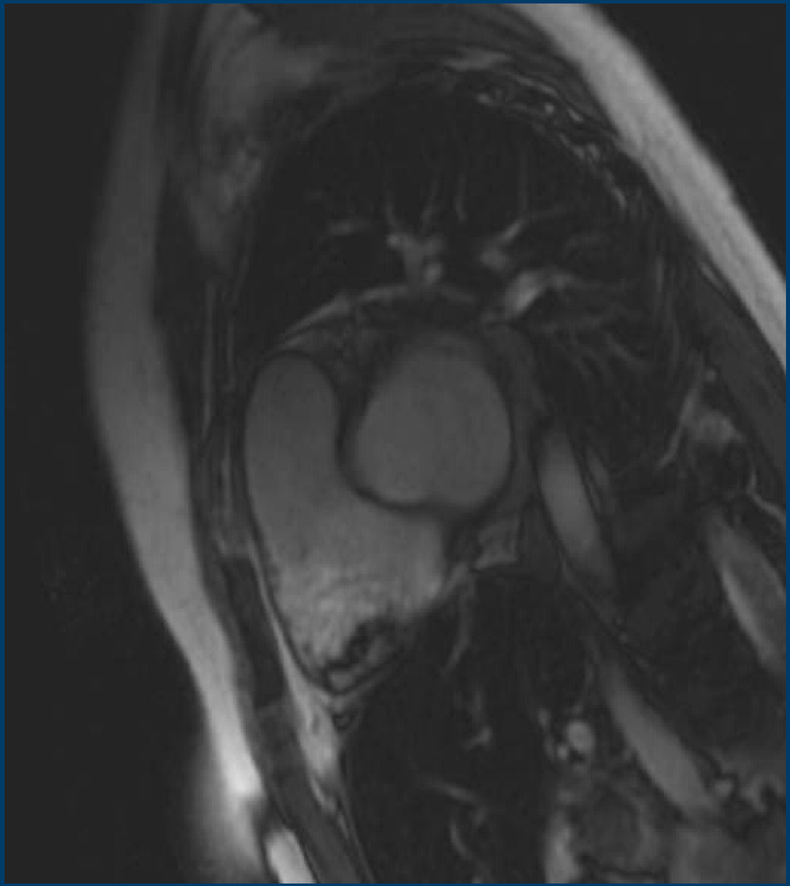
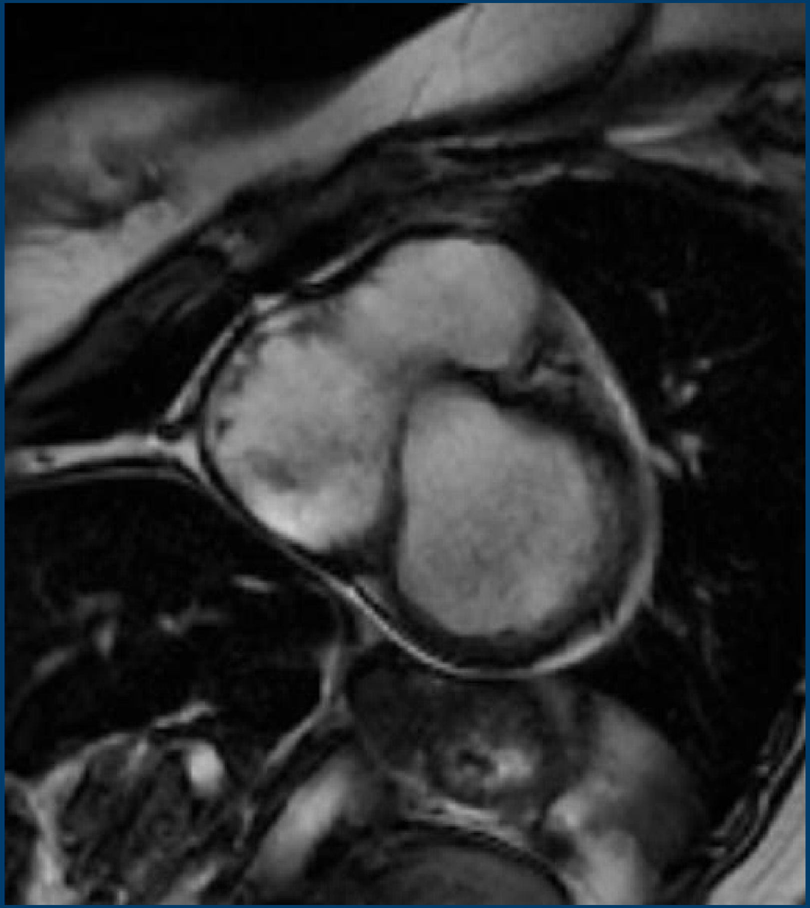


EF 56%; RVEF 51%

T2* 5.1ms



1 yr later LVEF 24%; RVEF 25%

T2* 6.6 ms

Four month follow-up

Initial:

- LVEF 24%; RVEF 25%
- Cardiac T2* 6.6 ms
- Liver R2* 1096 Hz

1-year follow up:

- LVEF 60%; RVEF 56%
- Cardiac T2* 6.5 ms
- Liver R2* 361 Hz

Thalassemia deaths in UK per 1000 patient years 1950-2003

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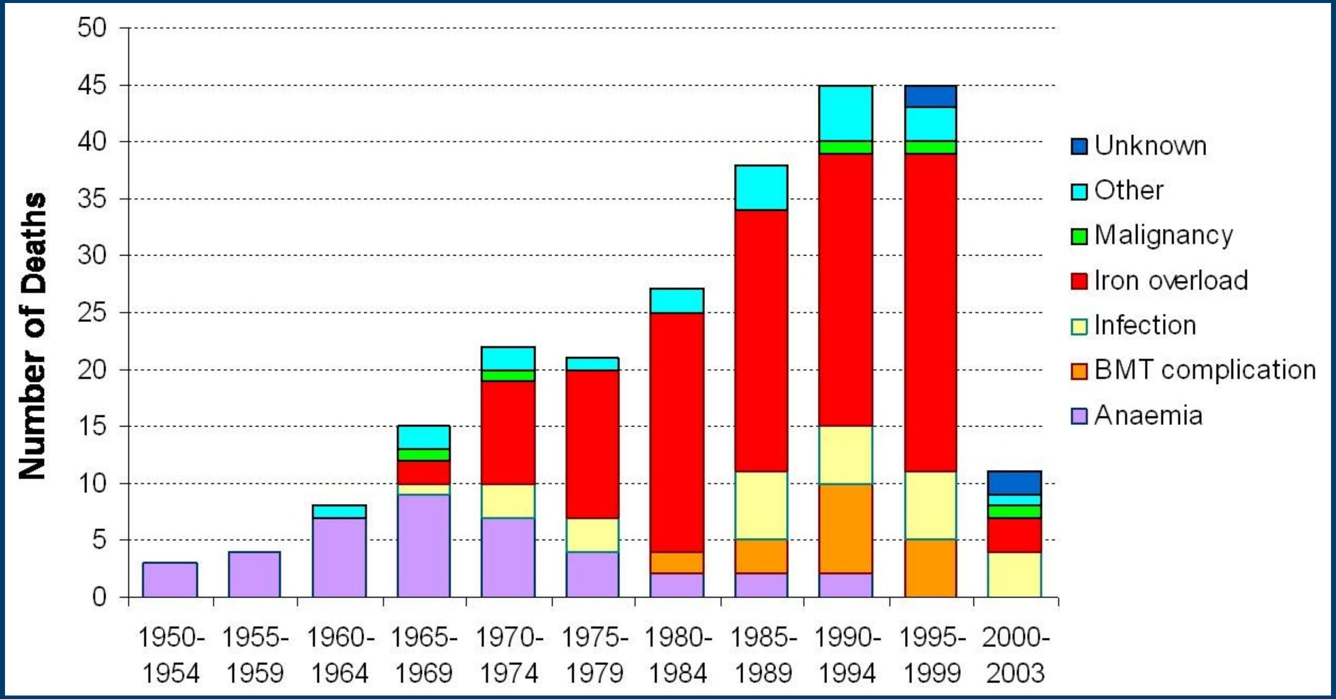

- Improved survival following bone marrow transplant
- Improved chelation therapy
- Decreased mortality from iron overload in older patients
  - T2* introduced in 1999

Modell B. Journal of Cardiovascular Magnetic Resonance 2008; 10:42.

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Iron Imaging techniques

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What does iron do to the MR field?

- Iron causes local field distortion
- Interaction between high-molecular-weight iron complexes (ferritin, hemosiderin and ferrioxamine) and water molecules causes T2 relaxation
  - Hemosiderin is the dominant storage form of iron and is predominantly what T2* measures
  - Enhances relaxation of water molecule protons buried in iron-containing proteins
  - Magnetic field gradients induced at the periphery of iron-containing proteins create loss of phase and relaxation enhancement of free nearby water protons
- Shortens T1, T2, T2* in proportion to iron deposition

Wood J.ASH Education Book December 10, 2011 vol. 2011 no. 1 443-450

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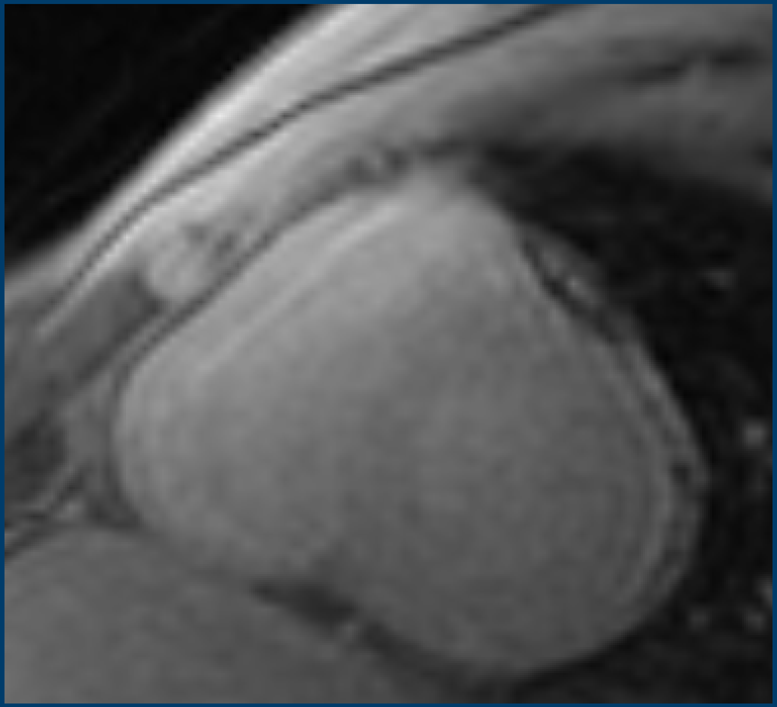
How do we image cardiac iron?

- T2* imaging
- Multiple gradient echo images with increasing echo times
  - Gradient echo preferred for cardiac T2*
  - Shorter acquisition time than spin echo
  - More prone to artifacts than spin echo
- ECG gating
- Ideally performed during one breath hold
  - Less artifacts from misregistration



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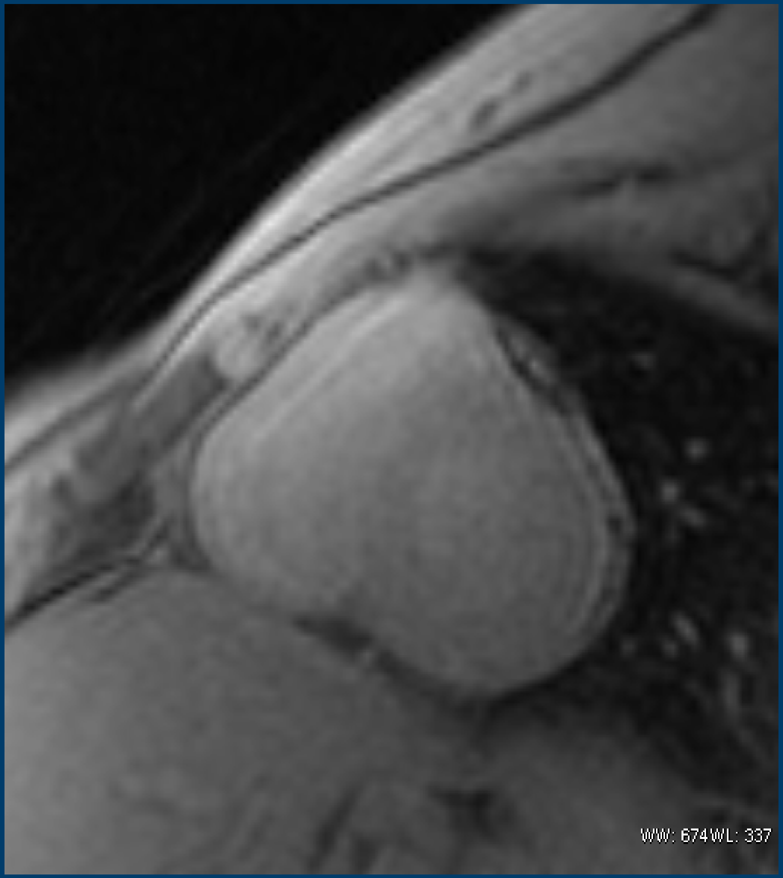
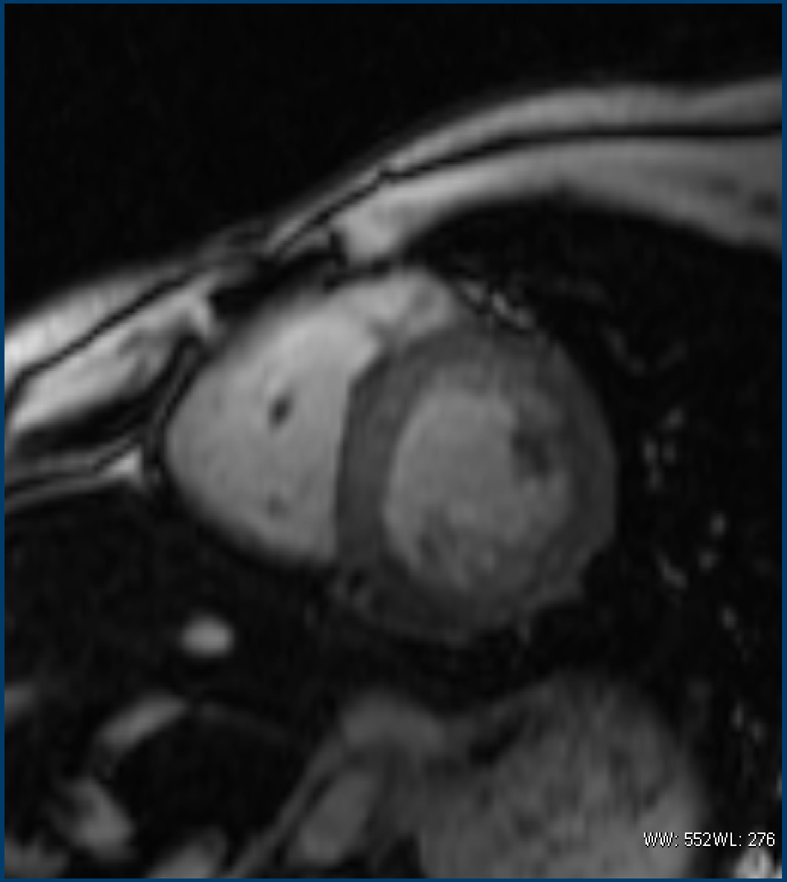
Cardiac T2*
Gradient echo sequence with multiple TE values



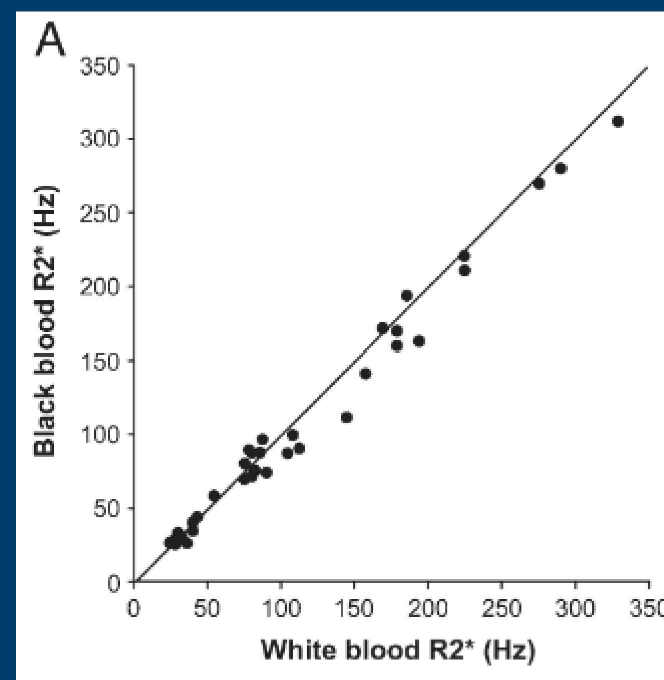
Normal volunteer T2* 40 ms



Thalassemia patient T2* 3 ms

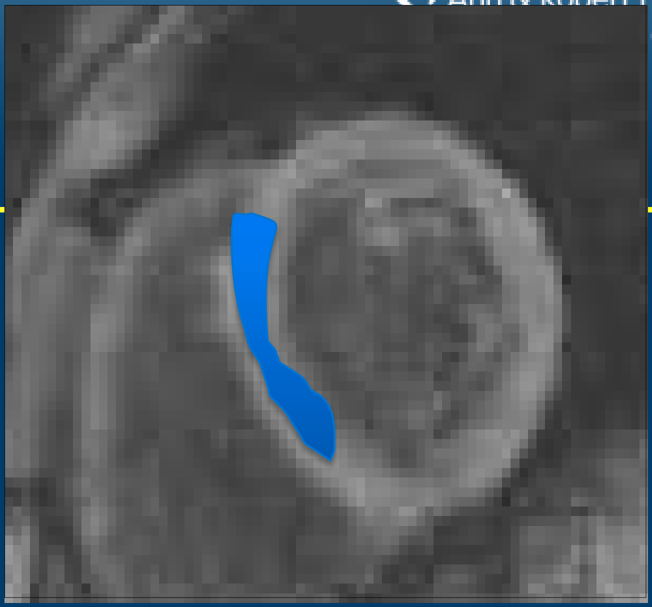
Cardiac T2* acquisition

- White blood
- Black blood prepulse
  - Good agreement between white and black blood T2*
  - Nulls blood pool
  - Improves within study reproducibility
  - Better interobserver agreement

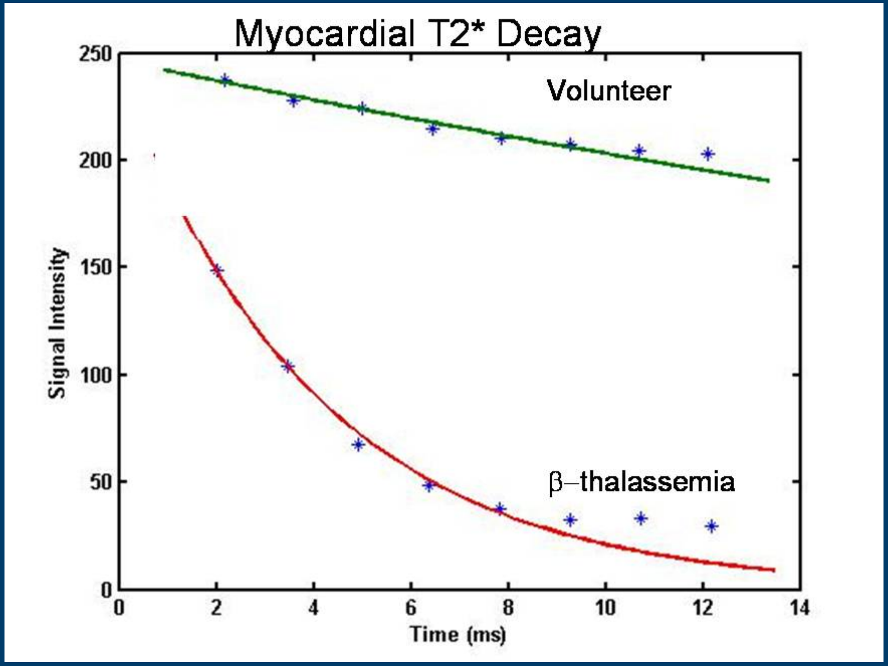


Ou P. Magnetic Resonance Imaging 30 (2012) 641–648

Cardiac T2* calculation



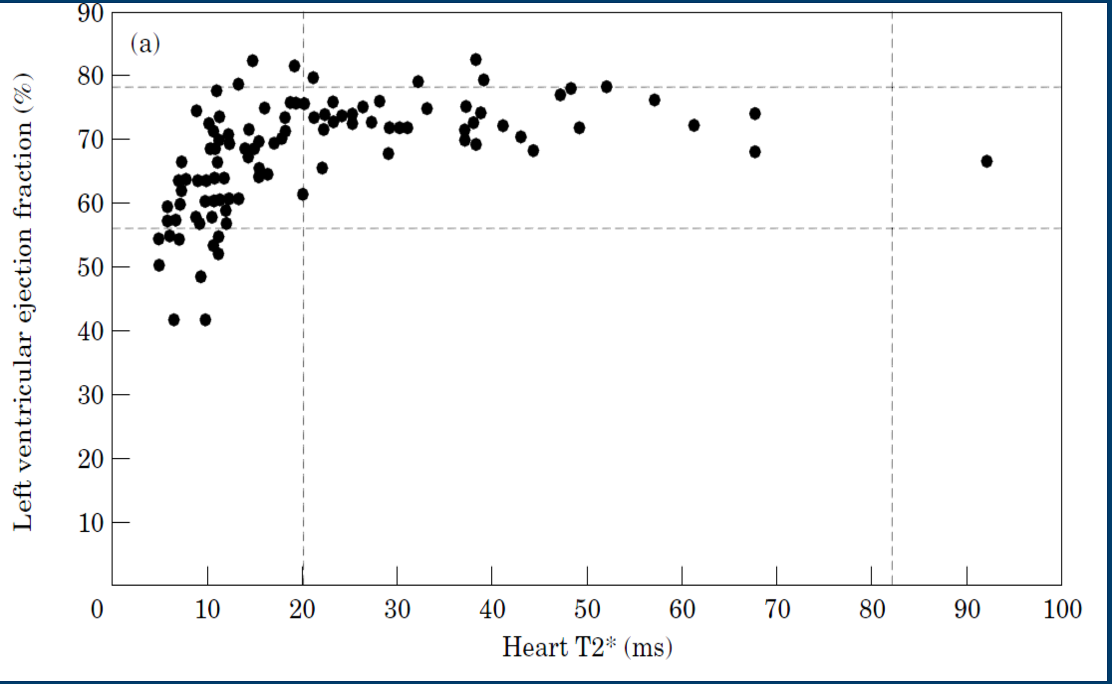
- Processing off-line
- Septal ROI drawn
  - Septal iron correlates with whole heart iron
- Decay of signal over multiple TE values fit to mono-exponential decay curve
  - $S(t) = S_0 e^{-t/T2^*}$
- Slope = 1000/T2*
- Higher iron content
  - Steeper curve and lower T2*



Pepe A. J Magn Reson Imaging 23:662–668

Cardiac T2*

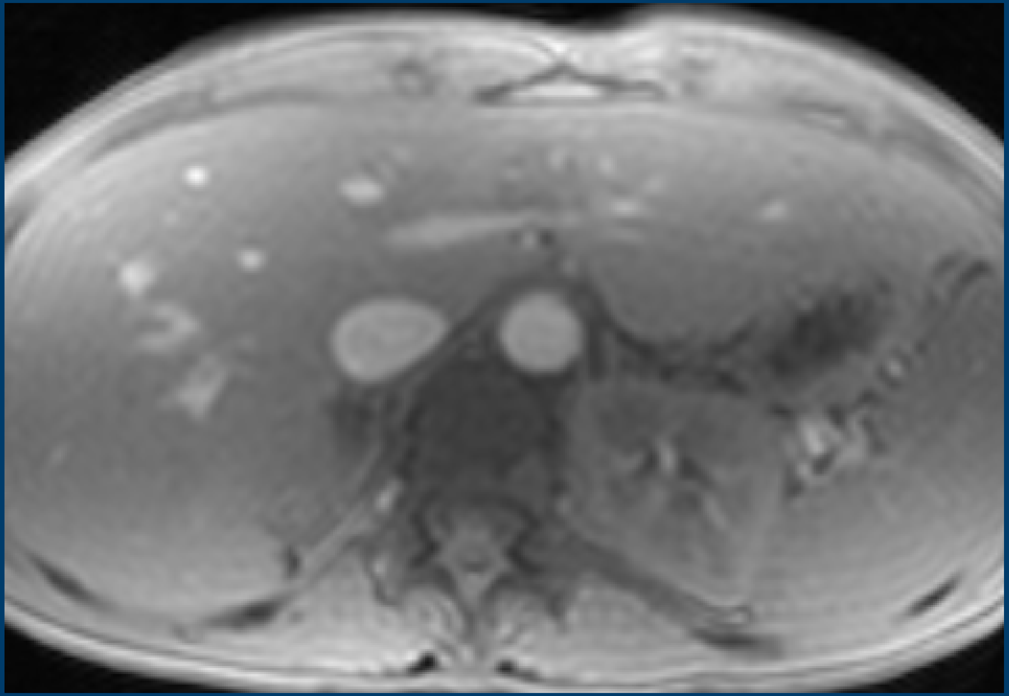
- Normal T2*
  - 52 +/- 16 ms (1)
  - 42.7 +/- 4.6 ms (2)
- Abnormal T2* = <20 ms
- Critical T2* = <8-10 ms
- T2* < 20 ms correlates with progressive decrease in LV ejection fraction ($p<0.0001$)



Anderson LJ, et al. Eur Heart J 2001; 22:2171-2179.
Storey P etal. Journal of Magnetic Resonance Imaging 2007; 25:540-547.

How do we image liver iron?

- T2* imaging
- Multiple gradient echo with increasing echo times
- Images acquired during one breath hold



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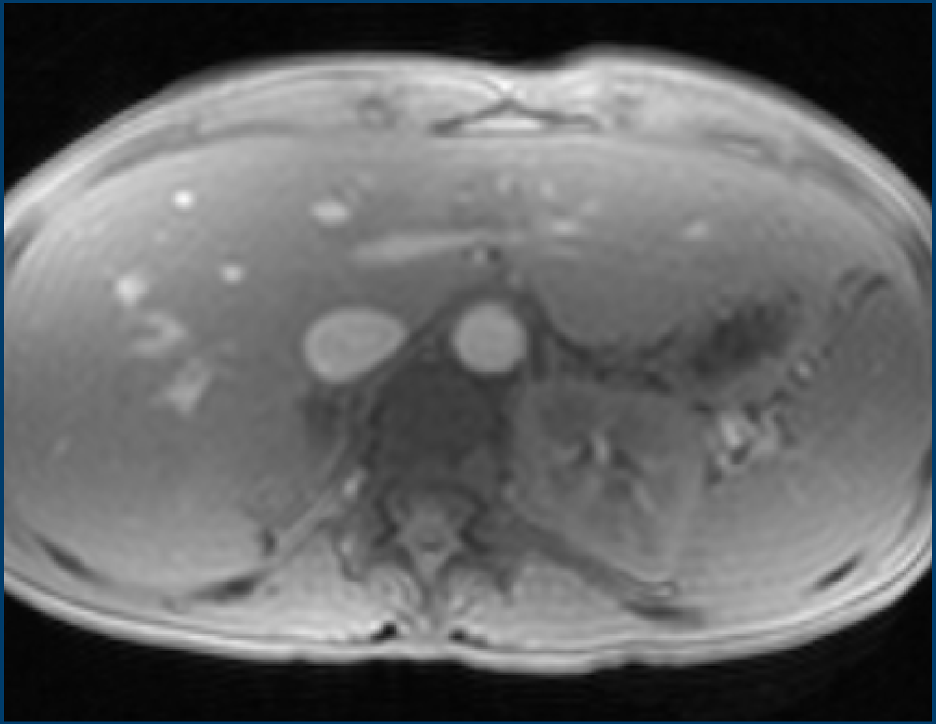
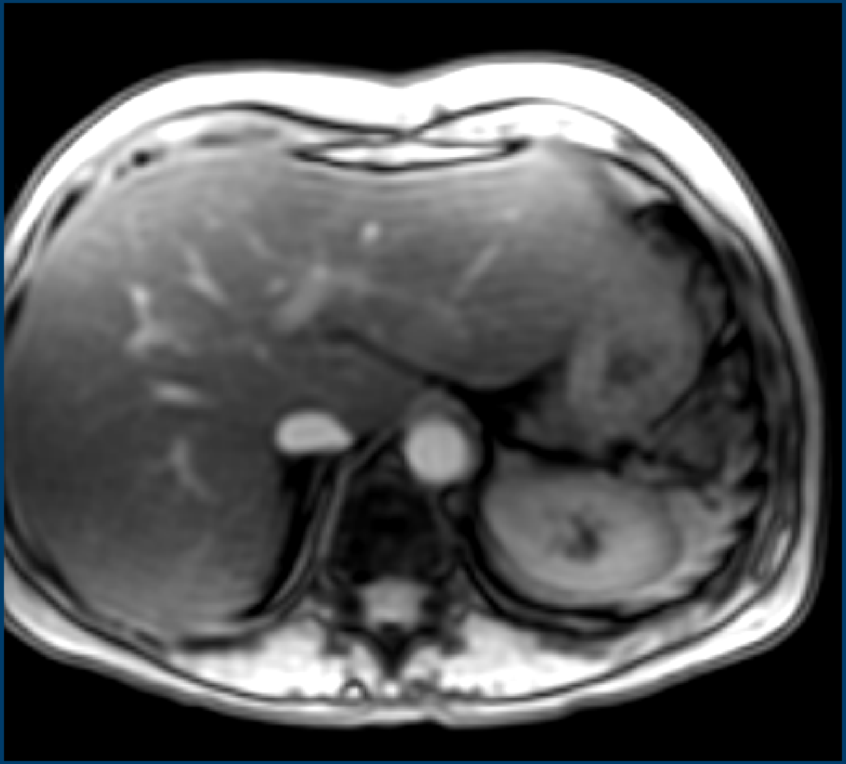
Liver T2*/R2*



Normal volunteer T2* = 33 ms

LIC = 1.04 mg/g dry weight liver



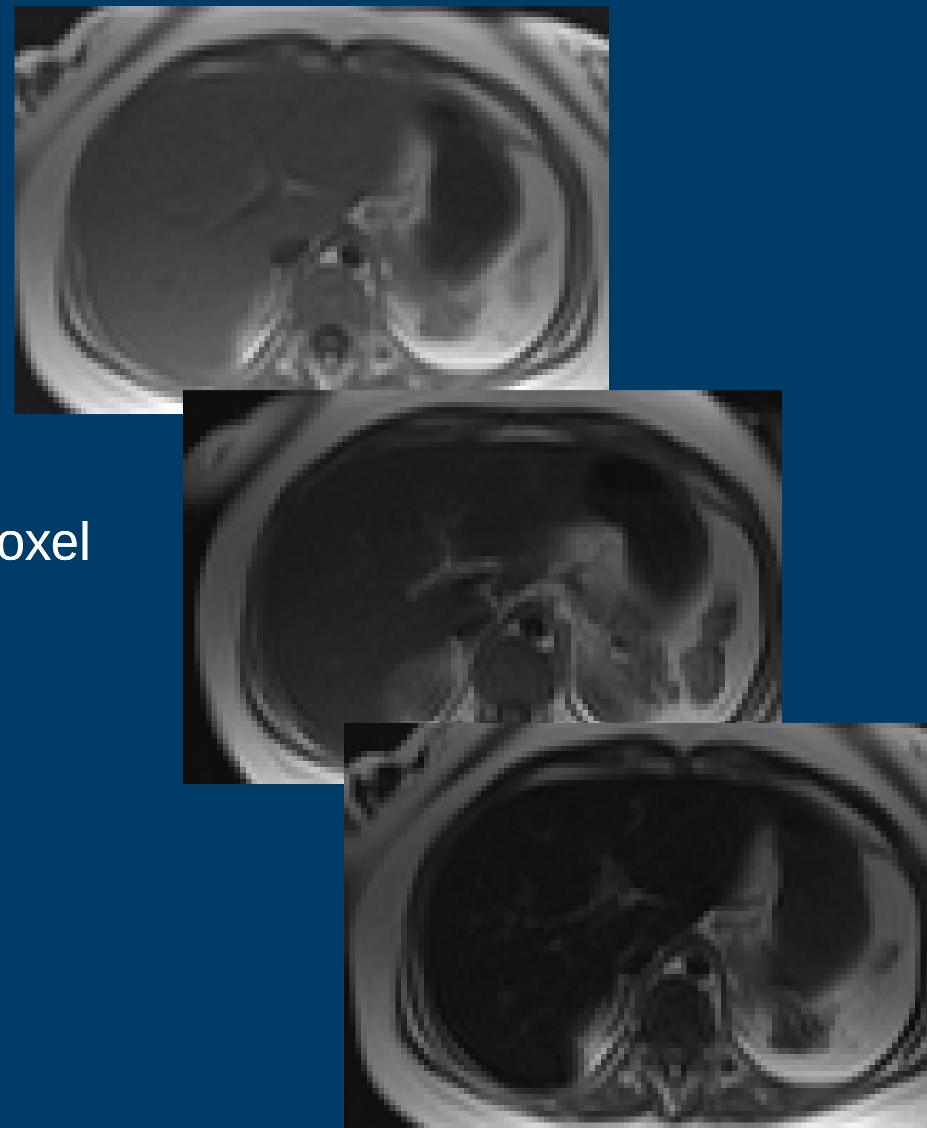
Thalassemia patient T2* = 2.1 ms

LIC = 12.5 mg/g dry weight liver

Wood JC, et al. Blood 2005; 106:1460-1465.

How do we image liver iron?

- T2 imaging
  - Multiple spin echo acquisitions
  - Fixed TR, increasing echo times
    - 6, 9, 12, 15 , 18 ms
  - 5-12 min
  - Breath holding is optimal
  - Less sensitive to size of imaging voxel and external magnetic influences



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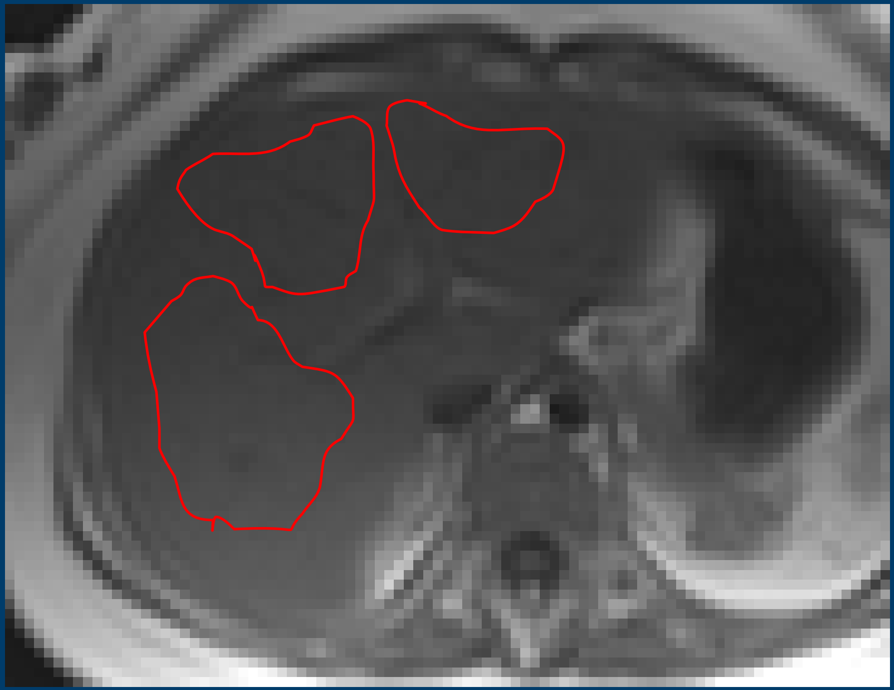
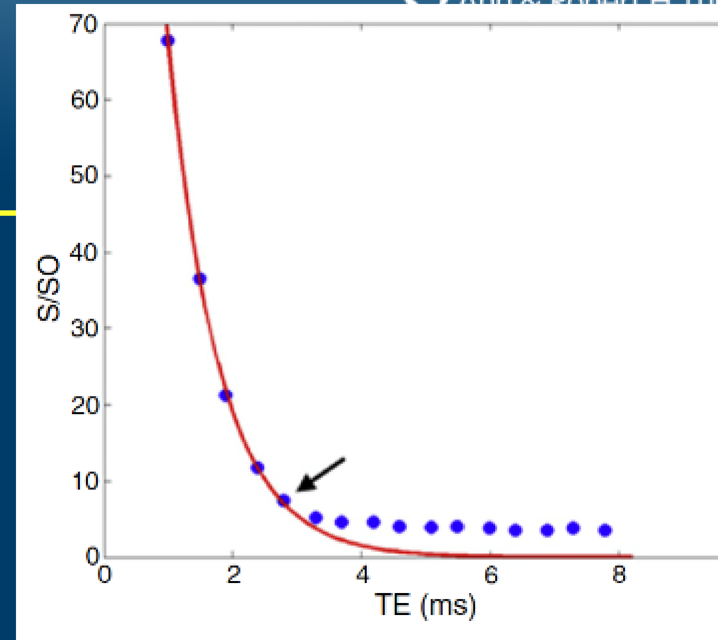
Liver R2* and R2 calculation

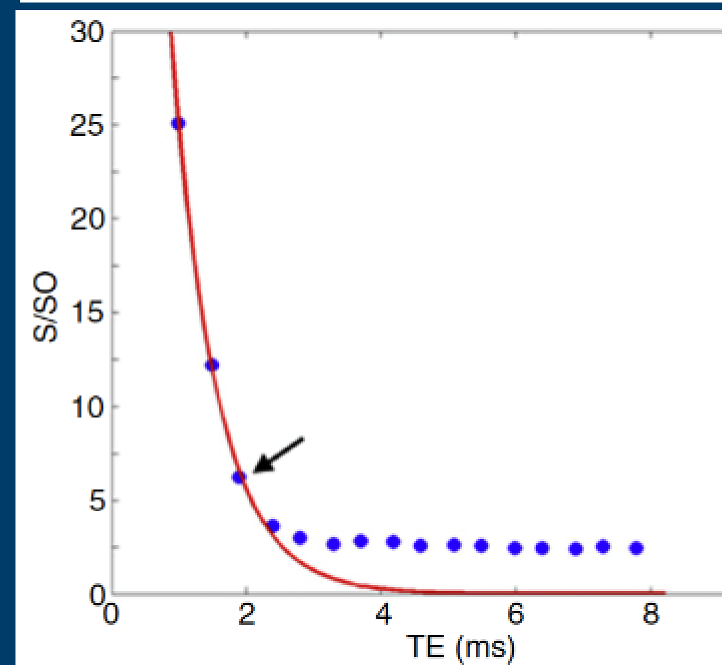
- Processing off-line
- One or multiple regions-of-interest (mROI) method
- ROIs placed on each liver slice avoiding hilar blood vessels



R2* and R2 calculation

- Averaged signal intensities for plotted as a function of TE
- R2* and R2 calculated by fitting the monoexponential equation
- S(TE)=S(0)Å~exp(− TE/T2*)
  - Nonlinear Levenberg– Marquardt algorithm
- Before fitting, noise baseline determined
  - Signal level off at increasing TE
  - Data points below twice noise level not included in fitting process





$$R2^* \text{ (Hz)} = 1/T2^*(\text{ms}) \times 1000$$

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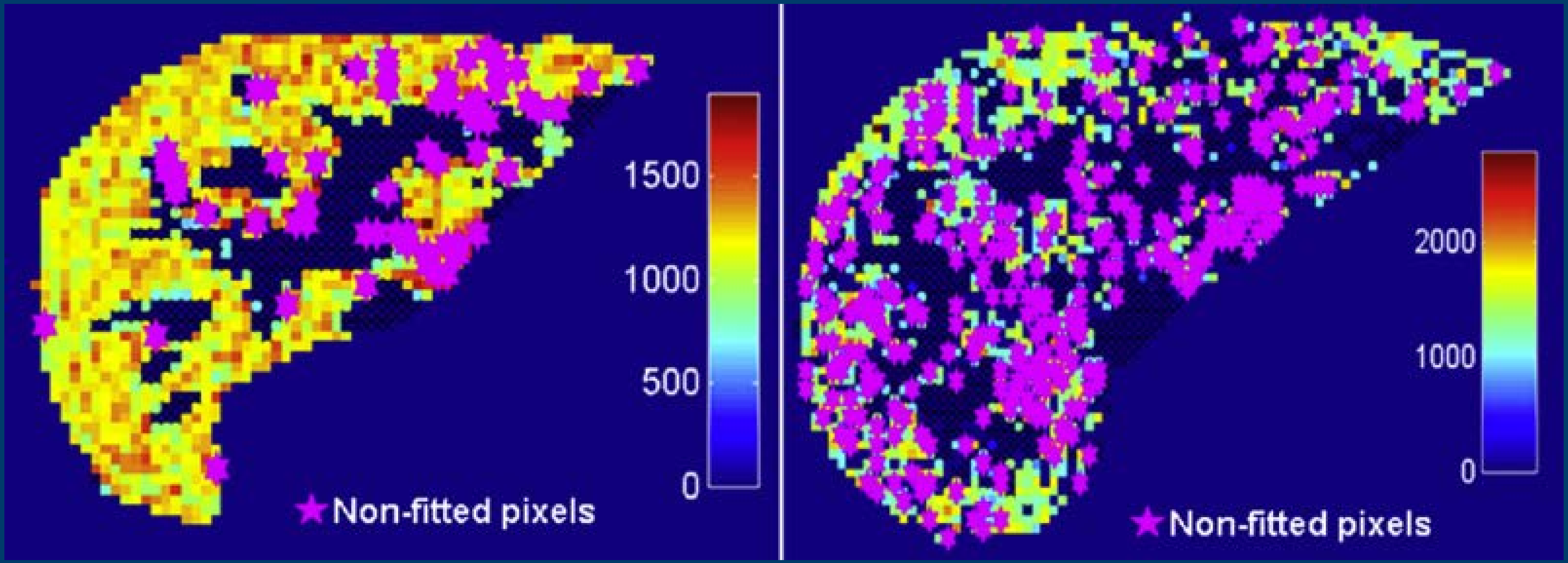
Liver R2 and R2* calculation

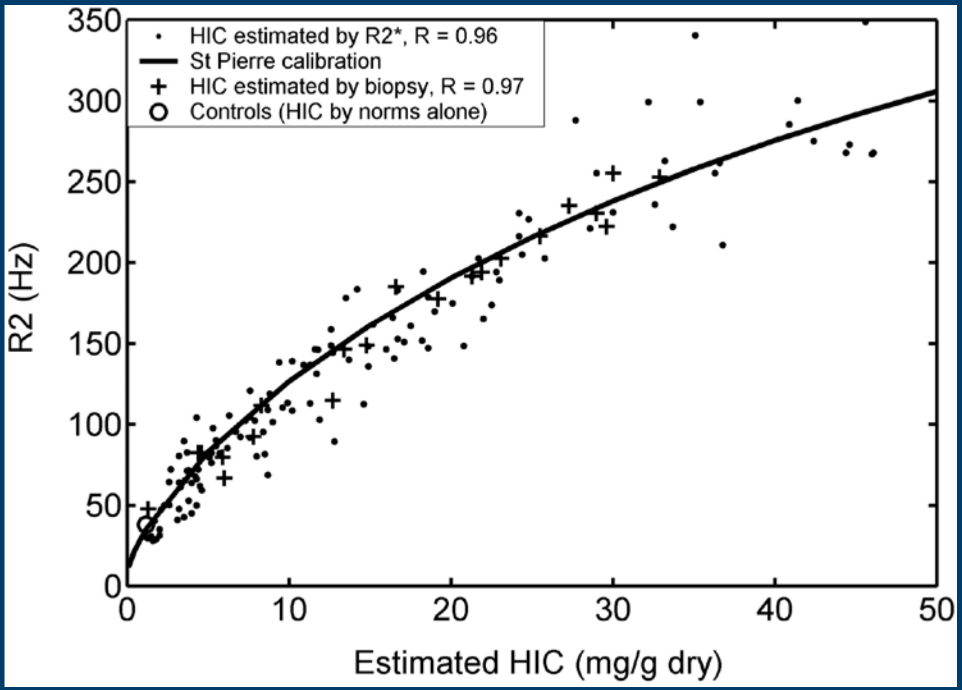
- Ideal method
- Extract vessels based on thresholding
  - Vessels have lower R2* compared to liver
- Detect non-fitted pixels and exclude from analysis
  - High iron or motion
  - Improved data reliability



Deng, Rigsby etal. MRI (3) 2012 799-806..

Liver iron concentration

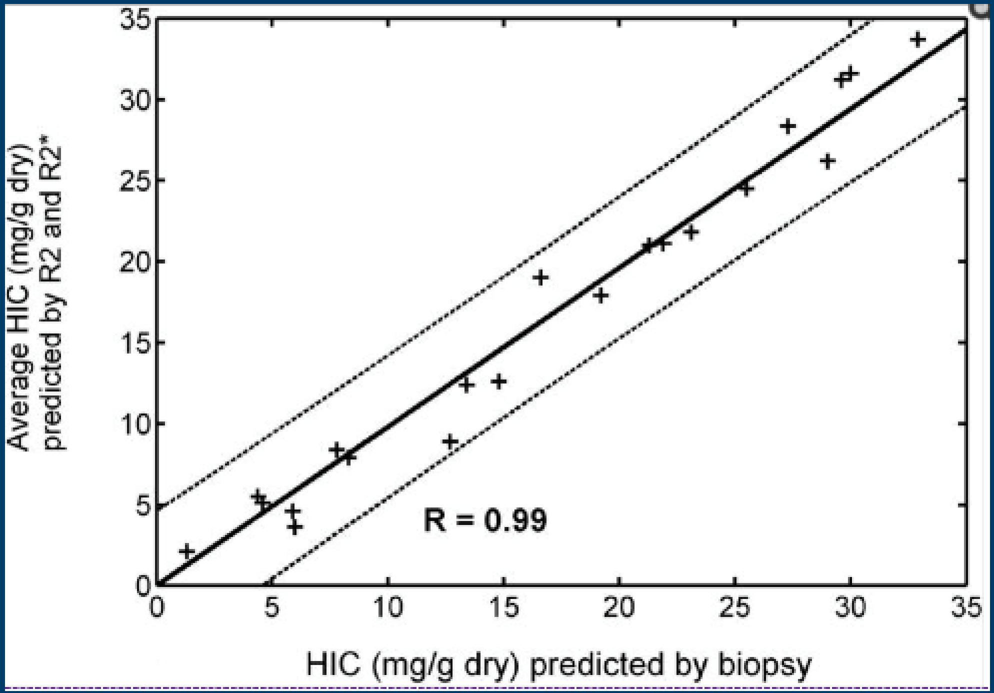
- Liver iron concentration (LIC) determined from calibration curve
- Agreement with liver biopsy for R2 (R=0.97) and R2* (R=0.96)
- Accurate c/w biopsy up to LIC 20-25 mg/g dry weight



Wood, J. C. et al. Blood 2005;106:1460-1465
Serai. Pediatr Radiol 2015; 45:1629–1634
Hankins. Blood. 2009;113:4853-4855

R2* and R2 agreement

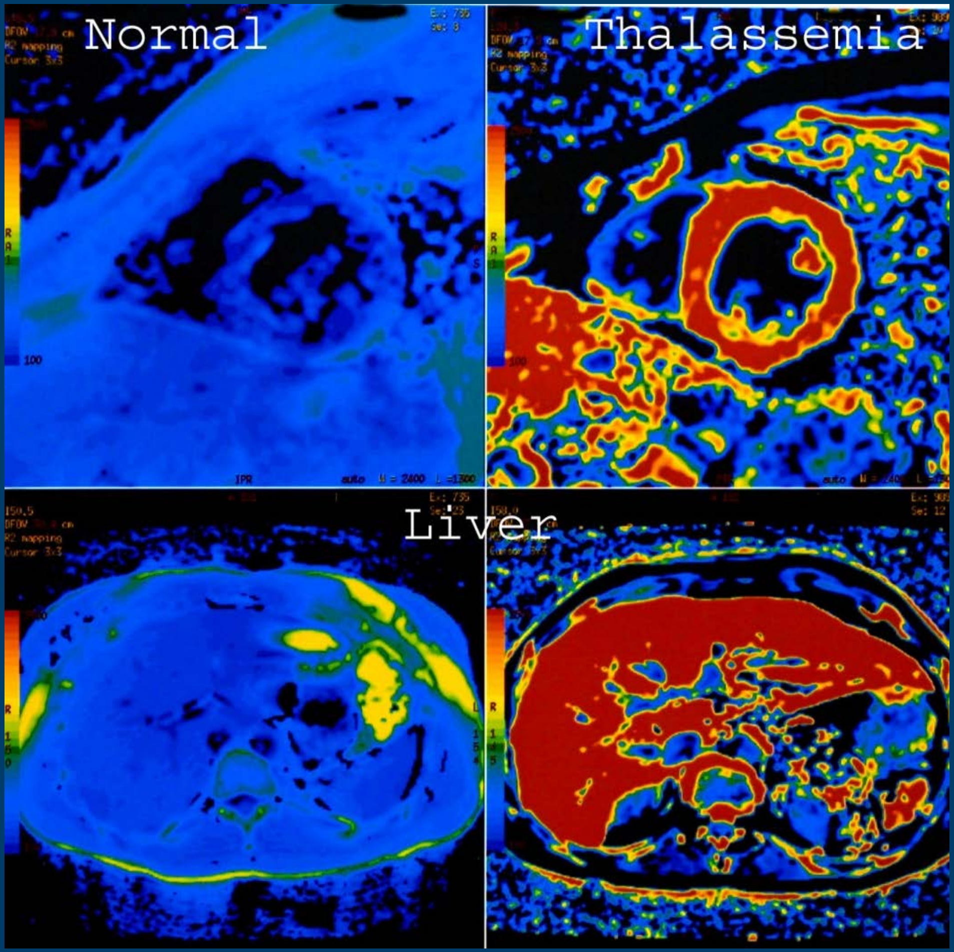
- Good agreement for LIC between R2* and R2
- Broad confidence intervals
- Variability increased with LIC >30 mg/g dry weight



Wood J. Blood. 2005 Aug 15; 106(4): 1460–1465.

Liver iron concentration

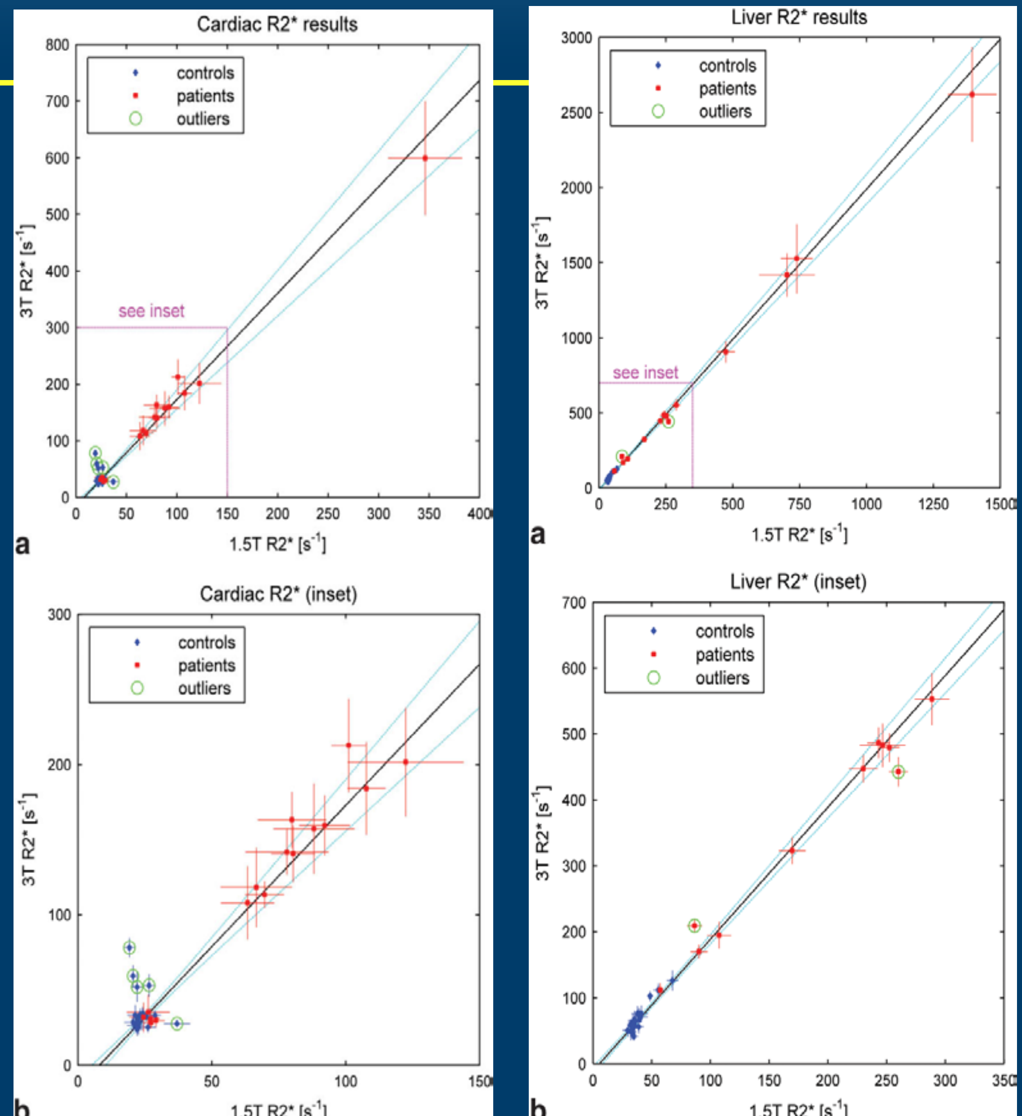
- No iron overload
  - T2* > 6.3 ms
  - R2* < 158 Hz
- Mild iron overload
  - T2* 6.3-2.7 ms
  - R2* = 158-370 Hz
- Moderate iron overload
  - T2* 2.7-1.4 ms
  - R2* = 370-714 Hz
- Severe iron overload
  - T2* <1.4 ms
  - R2* > 714 Hz



Chacko J, et al. Br J Haematol 2007; 138:587-593.

Iron Imaging at 3T

- Cardiac and liver R2* scale linearly with field strength
- Evaluated over a wide range of cardiac and liver iron concentrations



Storey P etal. JMRI 2007; 25:540-547

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T2* Reproducibility

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Cardiac and liver T2* reproducibility

- T2* values reproducible
  - 5 international sites scanned same patients
  - Coefficient of variation 5.9% heart, 5.8% liver

Kirk P etal. J. Magn. Reson. Imaging 2010;32:315–319.

FerriScan®

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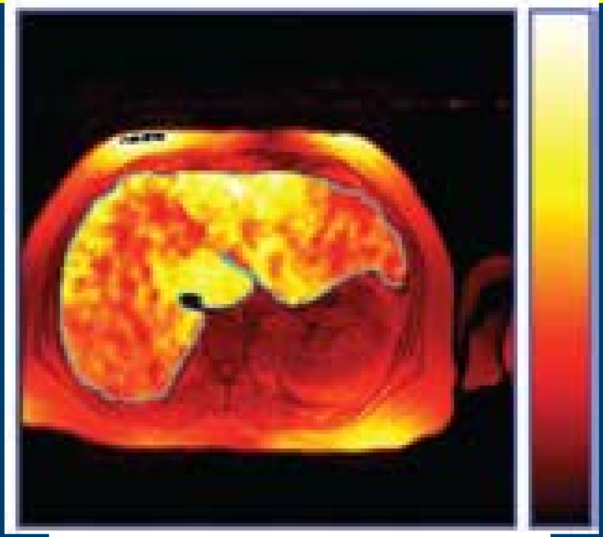
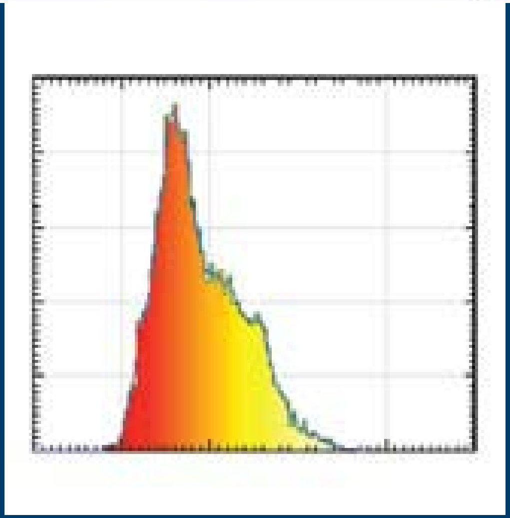
- Liver iron concentration calculation
- Resonance Health, Australia
- Provide specific acquisition technique
- Provide scanner validation
- Centralized data acquisition
- FDA approved
- Cost not paid by insurance





Mean LIC = 16.0 mg Fe/g dw

http://www.resonancehealth.com/ferriscan/Resources

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Iron imaging program

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Program Development

- MRI scanner software
  - 1.5T, 3T
- Multidisciplinary team
  - Physicist, Radiologist, Cardiologist, Hematologist, Research Associate, Nurse Specialist
- Post-processing software
- Means of assessing accuracy
  - Biopsy comparison, comparison with other center, iron phantom

Pediatric CV MR examination Iron overload cardiomyopathy

- Ventricular systolic function
- T2* liver and heart
  - Liver iron calculation
- Comparison with prior studies

MRI Assessment of Iron Overload

- Iron overload states
- Index iron overload case
- Iron imaging techniques
- MR iron imaging program

Thank you!