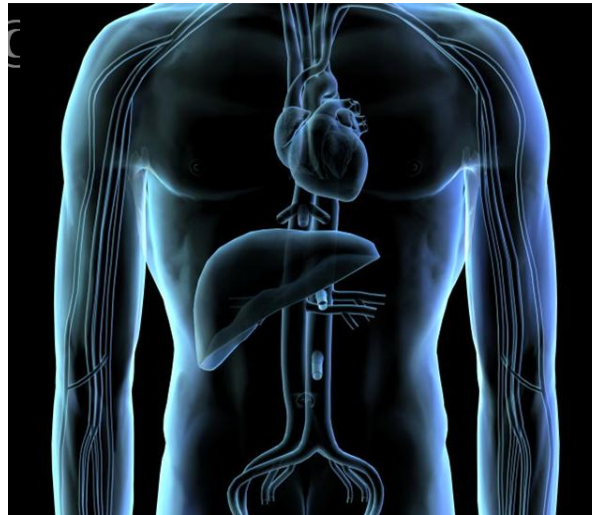


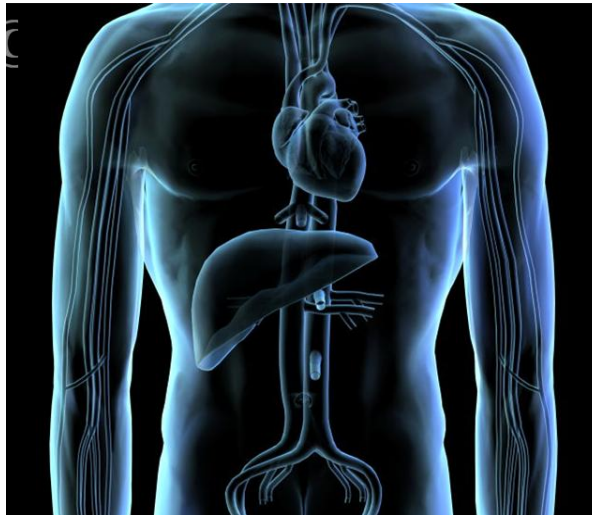
# Evaluation of Iron Overload

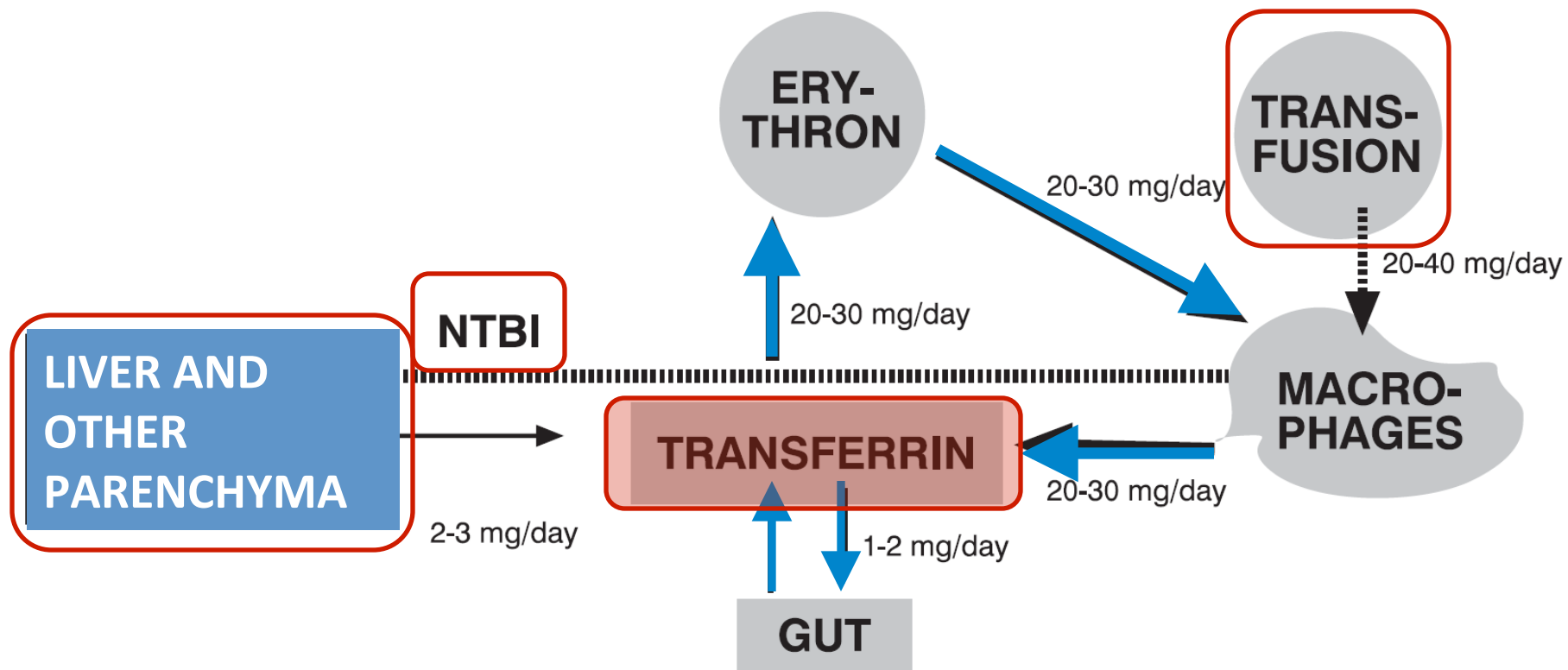


Madeleine Verhovsek MD FRCPC

Assistant Professor, McMaster University

Division of Hematology and Thromboembolism





# Serum Ferritin

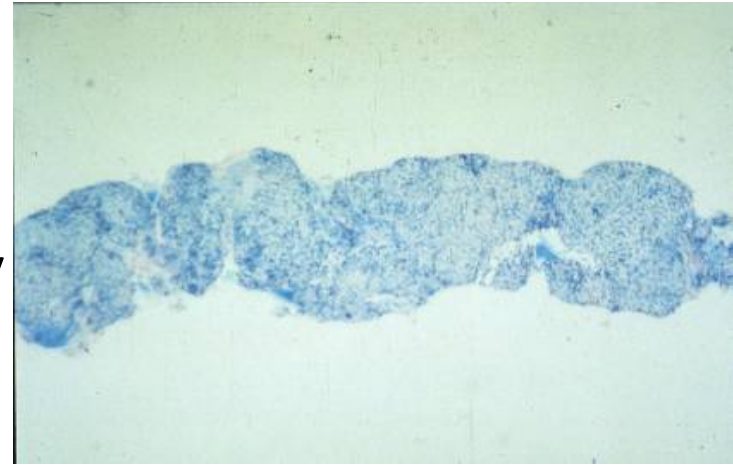
- < 3000 ug/L Ferritin secreted in iron-free form from macrophages
- > 3000ug/L Increasing proportion of iron-laden ferritin 'leaks' from hepatocytes
  
- Advantages for monitoring iron overload
  - Simple and widely available
  - Generally correlates with body iron stores
  - Associated with overall prognosis and cardiac disease in thalassemia major
  
- Can be unreliable
  - Day-to-day variations
  - False increases - inflammation, hepatitis and/or liver damage
  - False decreases - vitamin C deficiency
  - Underestimate of IOL in thalassemia intermedia

# Liver Iron Concentration

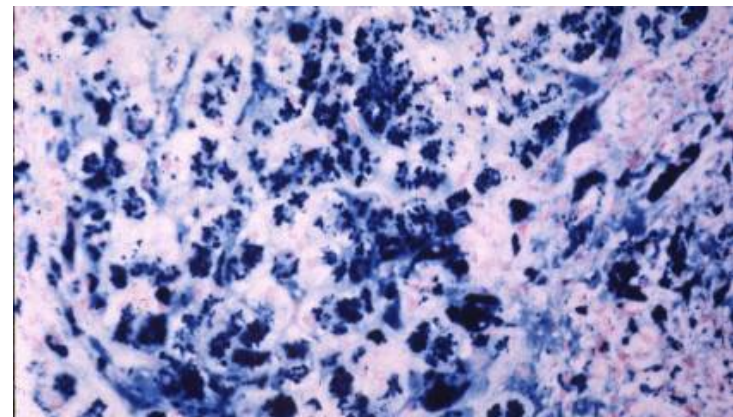
- Normal LIC = 1.8 mg/g dry wt
- < 7 mg/g dry wt seen in some non-thalassemic populations without apparent adverse effects
- LIC >15-20 mg/g associated with:
  - Worsening prognosis
  - Liver fibrosis progression
  - Liver function abnormalities

# Liver Biopsy

- Advantages
  - Direct measurement of LIC
  - Validated reference standard
  - Information on liver histology/pathology
  - Correlation with morbidity and mortality



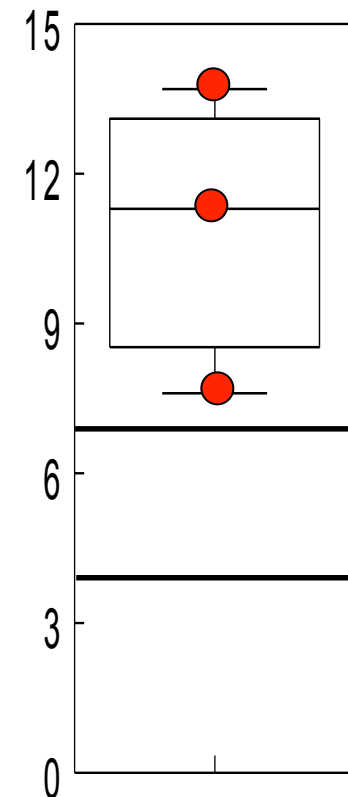
- Disadvantages:
  - Distribution artefact
  - Safety
  - Patient acceptance
  - Sample size
    - $\geq 1$  mg dry weight
    - $>4$  mg wet weight



Porter. *Br J Haematol.* 2001;115:239.

# Liver biopsy as gold standard?

- Six year old with transfusion-dependent  $\beta^+$  thalassemia and Gilberts, with symptomatic cholelithiasis
- At time of cholecystectomy, three separate liver pieces of adequate weight for analysis (>1 mg dry wt)
- Mean/SD: 10.8+/- 3.3
- 7.6, 11.3, 13.7 mg/g dry wt



# Noninvasive Measurement of Liver Iron

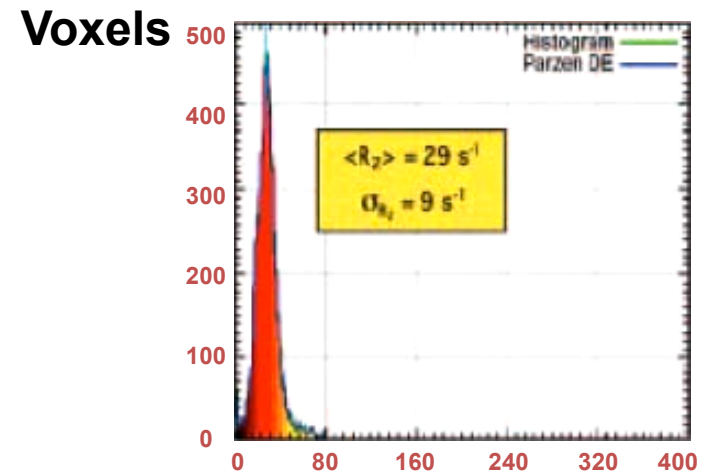
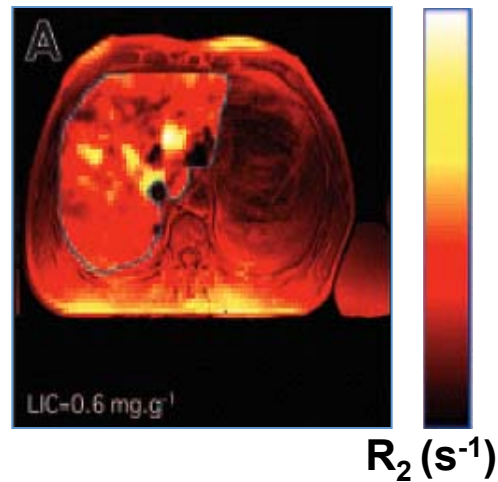
- SQUID (biosusceptometry of liver)
  - Only 4 in world. Well validated, but poor correlation with biopsy results.
- **MRI techniques**
  - Gradient echo (T2\*) (single breath hold)
    - Insensitive at levels >15 mg/g<sup>1</sup>
  - Spin echo (T2)(R<sub>2</sub>)
    - Linear over larger range, longer acquisition time of 20-40 minutes<sup>2</sup>
  - Gradient with Signal Intensity Ratio<sup>3</sup>
  - Spin echo with Signal Intensity Ratio<sup>4</sup>

MRI = magnetic resonance imaging; SIR = signal intensity ratio.

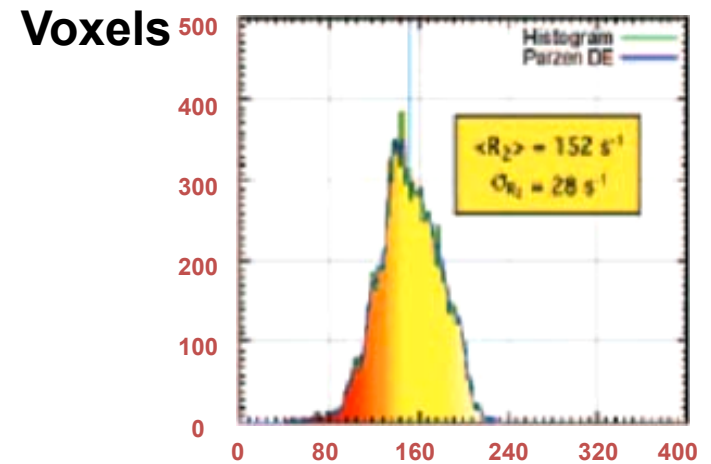
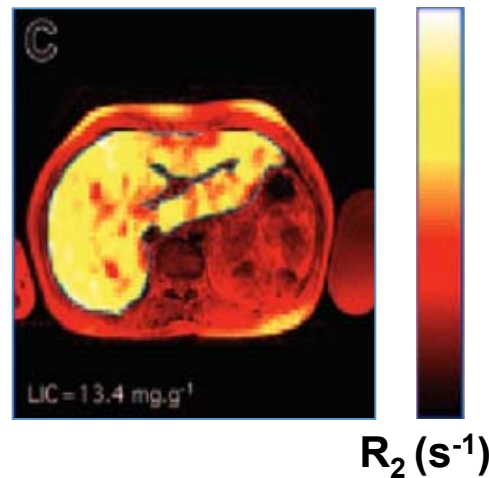
1. Anderson. *Eur Heart J.* 2001; 2. St Pierre. *Blood.* 2005; 3. Gandon. *Lancet.* 2004; 4. Jensen. *Blood.* 2003.

# R<sub>2</sub> Transverse Relaxation Rates

Nonoverload



Thalassemia major



“Ferriscan<sup>®</sup>”

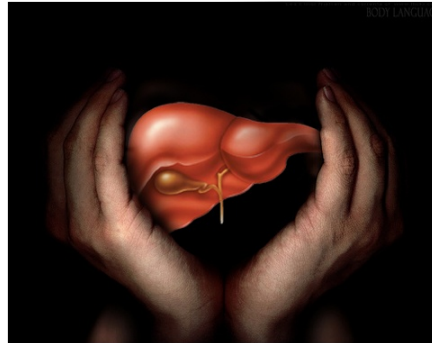
St Pierre et al. *Blood*. 2005;105:855.

Transverse relaxation rate R<sub>2</sub> (s<sup>-1</sup>)

# R2 Liver MRI – “FerriScan”

- MRI machine must be calibrated with a Phantom supplied by company
- Data sent via internet for analysis by Ferriscan software
- Payment per scan analysed
- Technique can be applied with little training, at any centre with a reasonably up-to-date MRI machine

# Limitations of Liver Iron Concentration (as a sole monitoring tool)



- ***Liver iron does not parallel heart iron***
  - Patients can develop heart failure with low levels of liver iron
  - Duration of exposure may be as important as maximum value?
  - Need to look at entire history of liver iron?
    - Hypothesis: If certain threshold never exceeded, unlikely that heart will accumulate iron

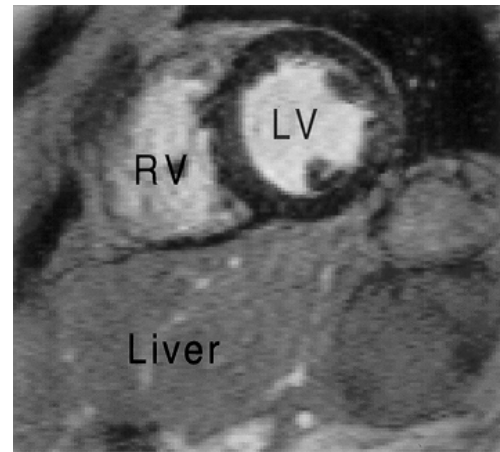
# Thalassemia and Cardiac Iron by T2\* proton MRI Liver & heart in same slice



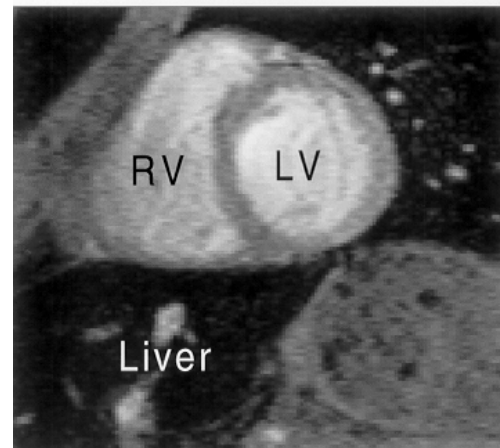
Children's Hospital, Boston; Andy Powell, MD

# Discordance of Liver and Heart Iron

**Severe cardiac iron  
Minimal liver iron**



**Severe liver iron  
Minimal cardiac iron**



# Cardiac Iron – T2\* MRI

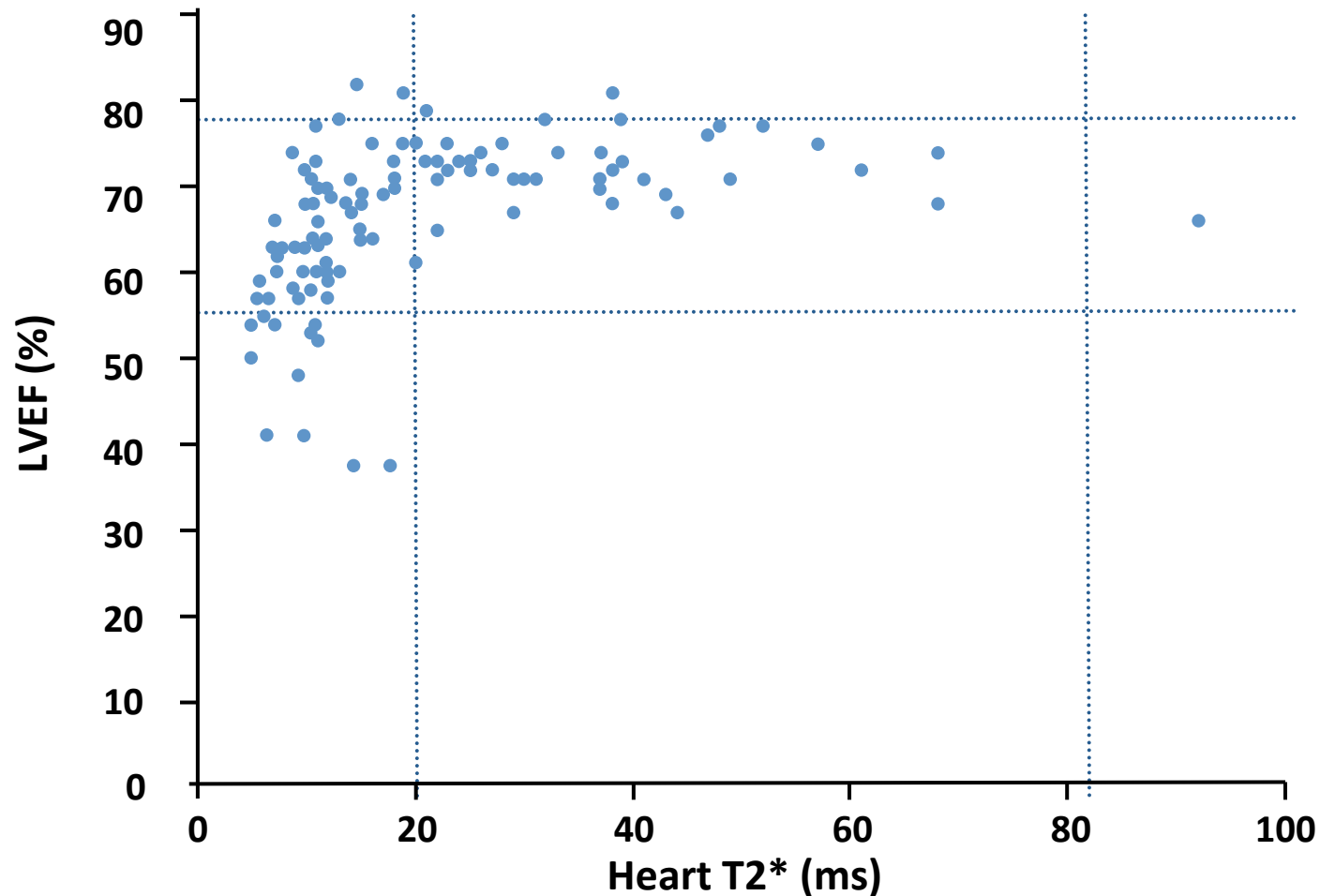
- Measures proton relaxation time in msec
- Shortened in presence of iron
- T2\* predicts risk of impaired left ventricular function

T2* Value	Risk of impaired LV function
>20 msec	Normal
10-20 msec	Up to 10%
8-10 msec	18%
6 msec	38%
4 msec	70%

- Disadvantages:
  - Requires expertise and standardization
  - Complex risk factors for developing heart failure
    - T2\* measures storage iron – not in itself directly toxic to cells
    - Other factors may increase labile intracellular iron (e.g. myocarditis, or lack of continuous chelation)

Anderson et al, 2001; Westwood, 2007

# Heart T2\* <20 ms Associated With Low LVEF; <8 ms highest risk

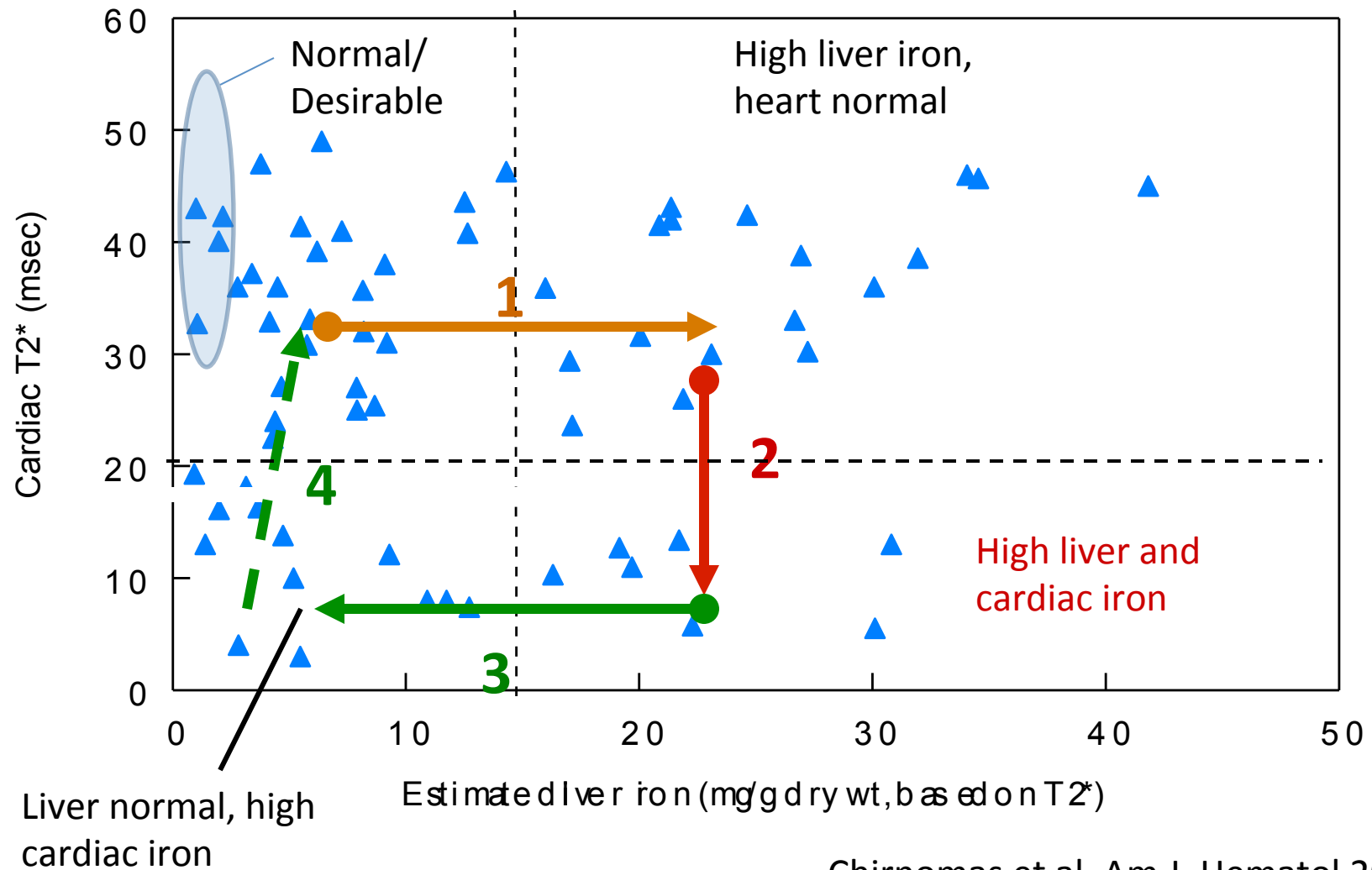


LVEF = left ventricular ejection fraction.

Anderson et al. *Eur Heart J.* 2001;22:2171.

# MRI Heart and liver iron assessment - "snapshot" view

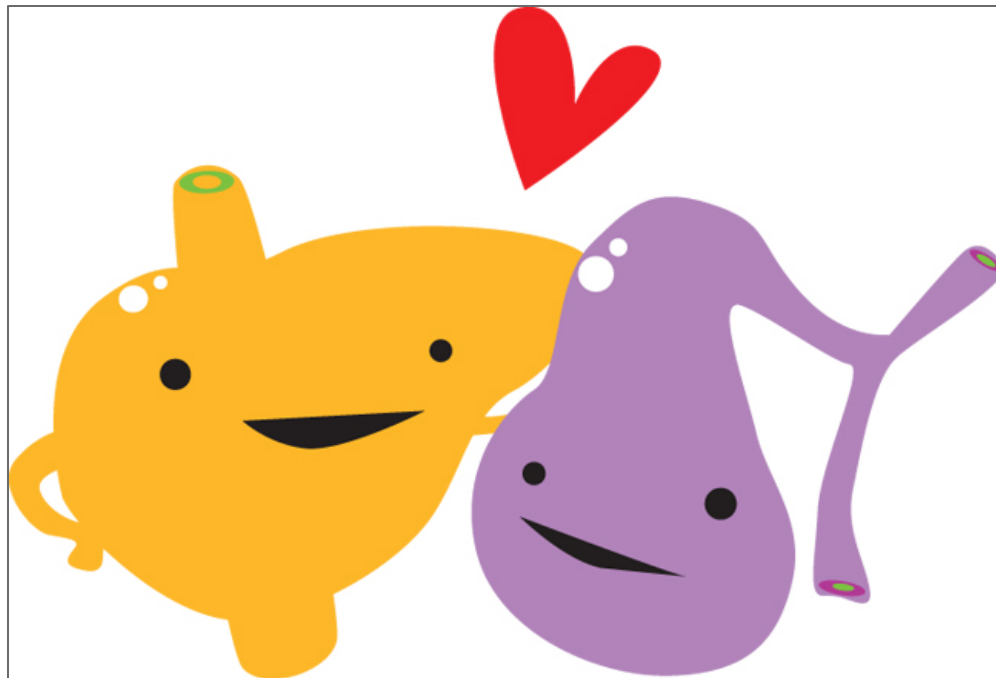
## Boston Children's data 2004-2007



# Other methods of measuring iron overload

- Urinary iron excretion
- NTBI or labile plasma iron assay

Thank you  
Questions?



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