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Spectrum of MR Imaging of Iron Overload:
Multi-system Imaging Findings and Quantification

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- **No financial disclosures**
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Objectives

- To familiarize the reader with the anatomic, physiologic and genetic considerations in assessment of systemic iron overload.
- To familiarize the reader with the radiographic patterns of system iron overload with specific emphasis on the MR Imaging distinguishing features in multi organ involvement.
- To review the preferred methodology for hepatic and cardiac iron quantification with Magnetic Resonance Imaging.

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Iron Overload

- Iron overload states may result in either hepatic parenchymal or reticuloendothelial deposition of iron
  - Hepatic parenchymal deposition of iron can occur in patients with cirrhosis and intravascular hemolysis
  - Iron overload from hepatic parenchymal deposition is usually distinguishable from chronic overload states related to multiple transfusions in which reticuloendothelial iron deposition occurs (as in patients with thalassemia)
- Hereditary hemochromatosis is an autosomal recessive disorder of iron metabolism characterized by excessive deposition of iron in multiple organ systems

Iron Overload

- Reticuloendothelial deposition
  - multiple transfusions
- Hereditary hemochromatosis
  - autosomal recessive
  - abnormal absorption of iron from the GI

Hemochromatosis

- Iron overload state
  - Heart
  - Liver
  - Pancreas
  - Skin

- Classic phenotype
  - Caucasian male 40-50 years old with “bronzed diabetes” and cirrhosis

Hemochromatosis

- #1 Autosomal recessive disorder
  - Typically Northern European ancestry
  - HFE gene (C282Y mutation)
  - 1 in 250 Caucasians are homozygotes

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NEJM 2008;358:221-230

Question #1

- What percentage of individuals with homozygous HFE genes will have symptomatic hemochromatosis?
  - A. 100%
  - B. 75%
  - C. 25%
  - D. 1%

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Hemochromatosis

- Not all homozygotes manifest disease
  - 28% men
  - 1% women
- True incidence of symptomatic hemochromatosis is unknown

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NEJM 2008;358:221-230

Hemochromatosis: Presentation beyond “bronzed diabetes”

Common symptoms:

Fatigue

Malaise

Arthralgia

Heart disease:

Presenting symptoms in 15%

Niederau C, et al. Adv Exp Med Biol 1994;365:293
Edwards CQ, et al. NEJM 1993;328:1616

Cardiac Involvement in Hemochromatosis

- **Cardiac Function**:
  - Diastolic dysfunction
  - Restrictive physiology with bi-atrial enlargement
  - Dilated cardiomyopathy
  - Biventricular failure

- **Arrhythmias**:
  - Conduction system disease (AV node)
  - Tachyarrhythmia (atrial & ventricular)

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Hemochromatosis: Lab evidence of abnormal iron stores

- **Elevated <u>serum ferritin</u>**
  - > 250 ug/L in men
  - > 200 ug/L in women

- **Elevated <u>transferrin saturation</u>**
  - > 60% men
  - > 50% women

95% Accuracy for diagnosis

Niederau C, et al. Adv Exp Med Biol 1994;365:293
Edwards CQ, et al. NEJM 1993;328:1616

Iron Overload: CT Findings

- Increased attenuation of the liver
- 75 to 130 HU
- Non-specific findings, also seen in:
  - Wilson's disease,
  - Gold deposition,
  - Type IV glycogen storage disease
  - Amiodarone administration

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Iron Overload: MRI Findings

- More specific than CT
  - Due to paramagnetic susceptibility effects of iron
    - Iron shortens T1, T2 and T2*
- T2*-weighted gradient most sensitive to paramagnetic susceptibility artifacts from Iron
  - TE of 15 - 25
  - Flip angle of 10 - 30 degrees
  - Maximizes the T2* effects and provides optimal imaging

Iron Overload: MRI Findings

- T2 is the “natural” time constant for decay or dephasing of transverse magnetization
- However, decay occurs much faster than would be predicted
- T2* can be considered the “effective” or “observed” T2 and is always less than the T2 constant for decay
- T2* results from inhomogeneities in the magnetic field, as can be seen or accentuated in states of abnormal iron deposition

Iron Overload: MRI Findings

- **Calculate T2 and T2* in ms**
- **Reciprocals of T2 and T2* can also be measured as:**
  - **R2 (1000/T2) and**
  - **R2* (1000/T2*) and**
  - **Have been shown to demonstrate a linear relationship with iron concentration**

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

Iron Overload: MRI Findings

- **Hepatic Iron measured on T2* images at 1.5 T:**
- **> 20 ms = normal**
- **< 10 ms = abnormal iron deposition**
- **@ 3 T – use value of 6-7 ms as cut off for iron deposition**

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Hepatic R2*

- **1000/T2***
  - **Units of Hertz**
- **Larger the R2*, the greater the amount of iron**
  - **Measurements are dependent on field strength of the magnetic and can vary**
  - **50-75 Hz (mildly increased)**
  - **90-200 Hz (moderately increased)**
  - **>300 Hz (severely increased)**

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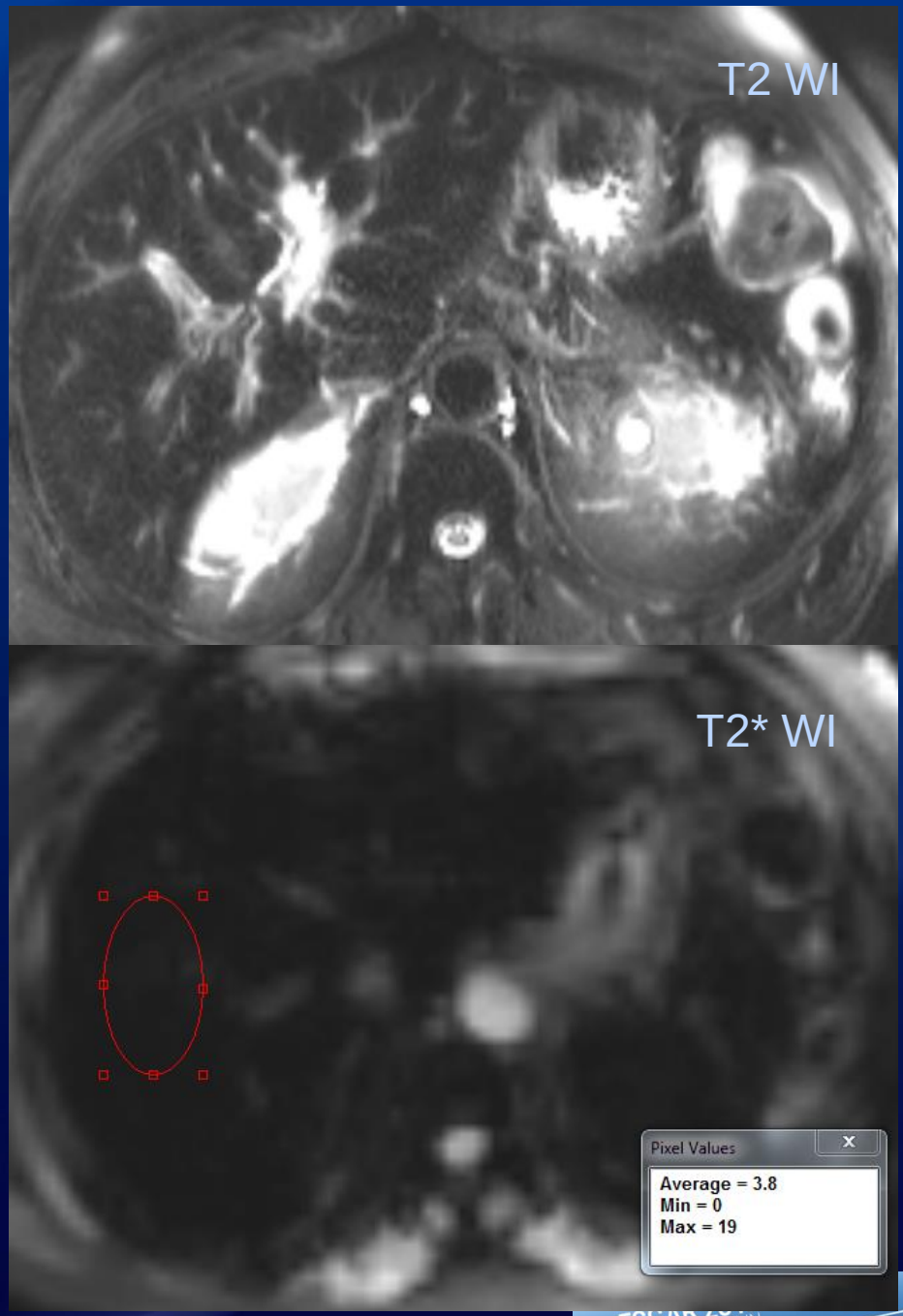
T2* Calculation

- Measured by placing an ROI on T2* WI
- This liver demonstrates severe decreased SI on T2 WI due to Iron deposition
- T2* WI show a T2* of 3.8 consistent with severe abnormal iron deposition



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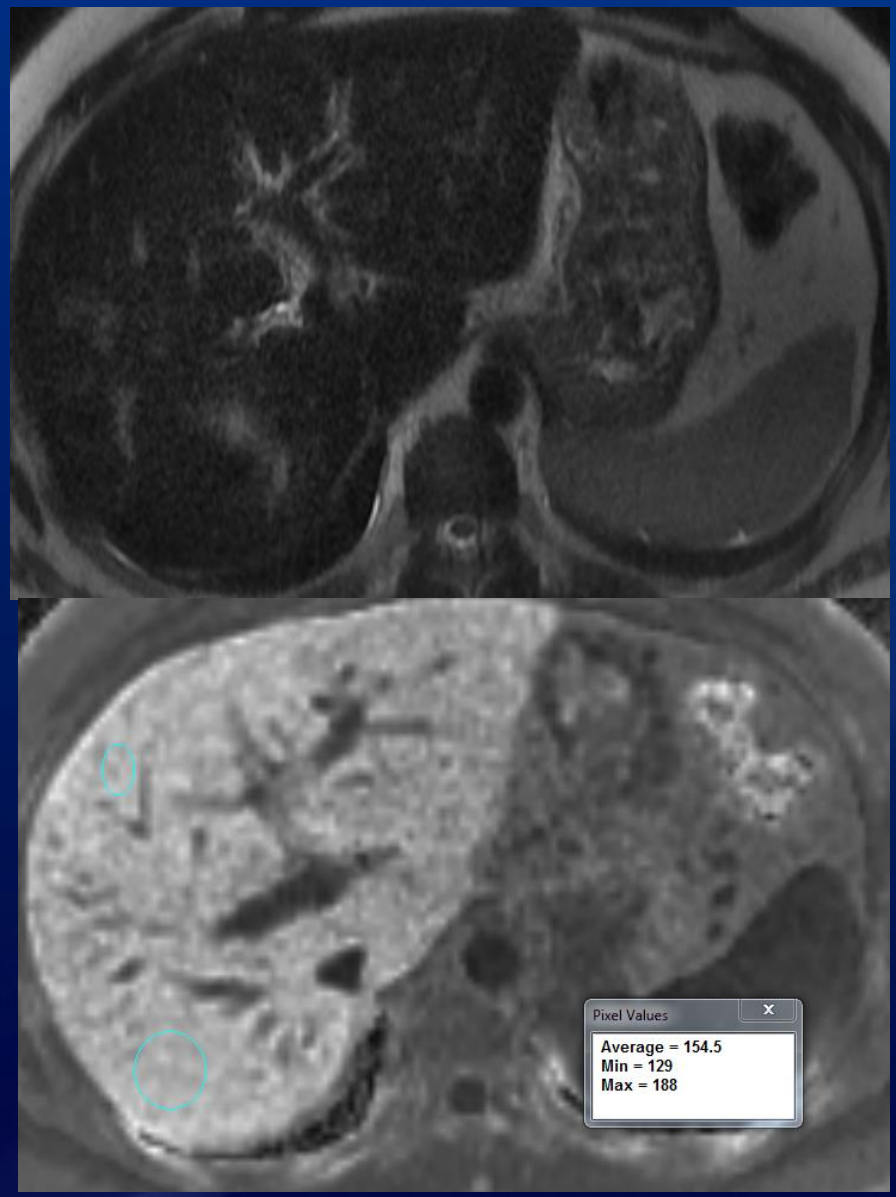
R2* Calculation (1000/T2*)

- 41-year-old gentleman with hereditary hemochromatosis, positive homozygous for C282Y gene mutation, treated with phlebotomies
- R2* of 154 is indicative of abnormal iron deposition @ 1.5 T



Iron Overload: MRI Findings

- Hereditary hemochromatosis
- SI changes in other organs
  - Pancreas, myocardium, adrenal glands, skin and other endocrine glands
- Transfusion-related iron overload
  - Abnormal SI only in RE system
    - Liver, spleen, bone marrow

Hepatic Iron Overload
Case Presentation: Case 1

- 47-year-old gentleman with hereditary hemochromatosis presents for follow up imaging of the liver

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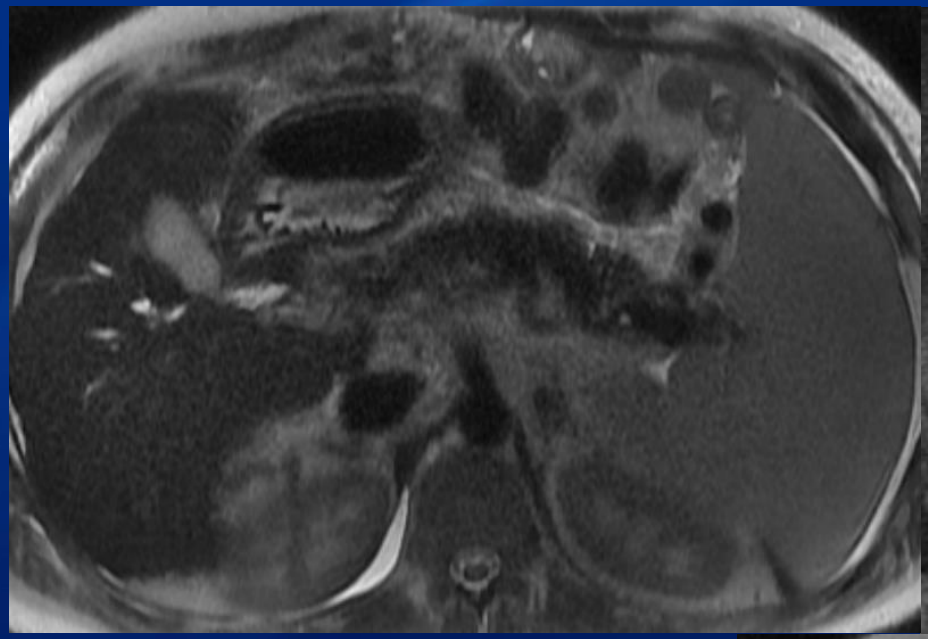
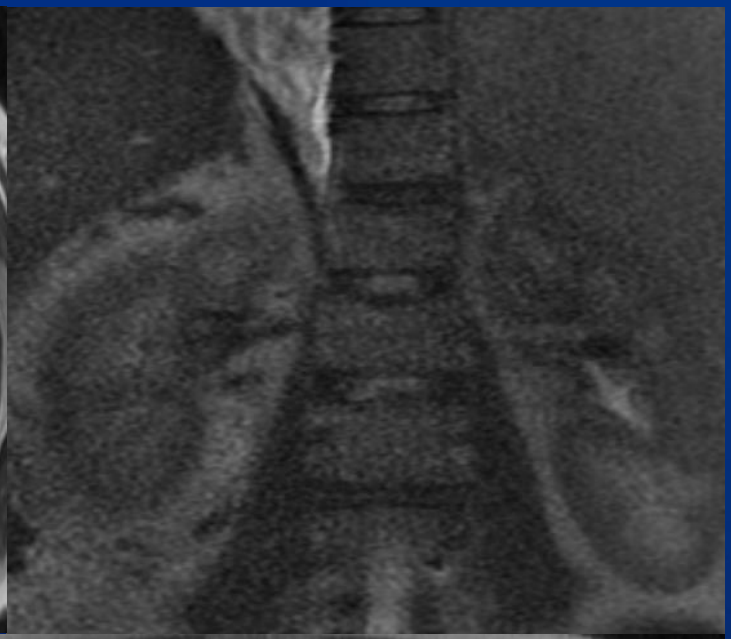
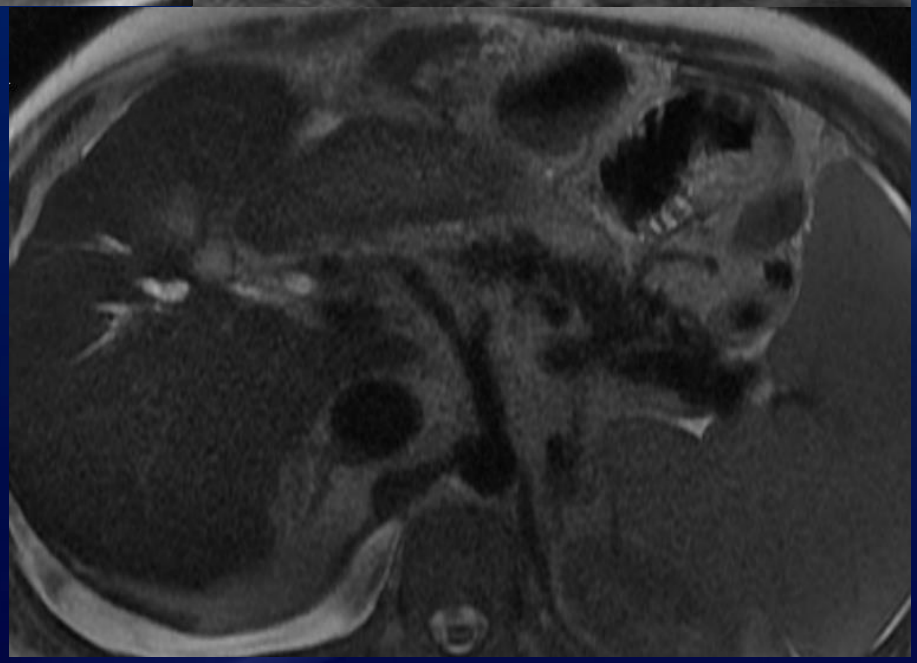




- MR imaging shows markedly decreased SI in the liver (T2* was markedly abnormal) with profound decrease SI also noted in the pancreas and adrenal glands



Gross Pathology:

- Pathologic gross specimen of liver ex-plant at the time of orthotopic liver transplantation.
- Specimen shows marked nodularity and cirrhosis with discoloration of the liver due to abnormal iron deposition

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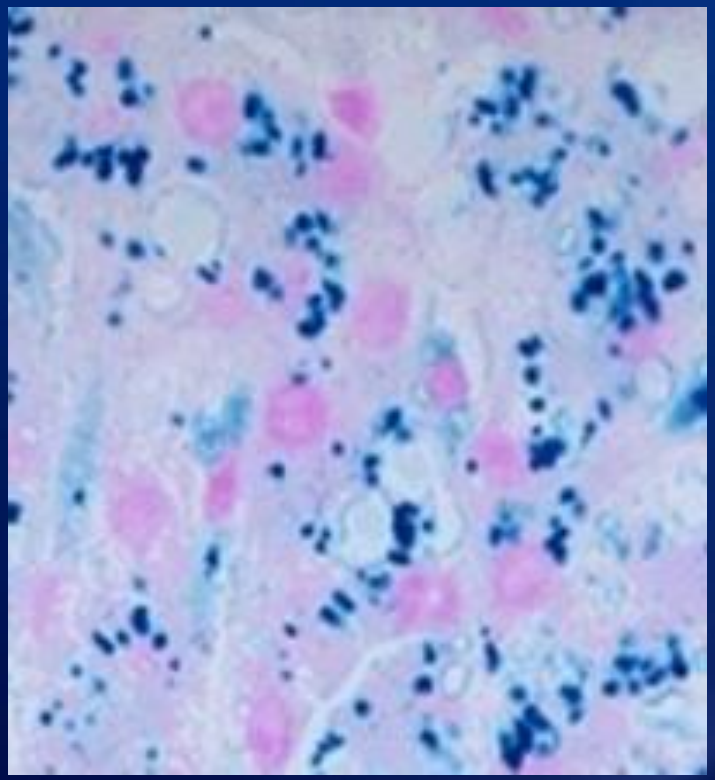
Histopathology:

- Prussian blue stain reveals abnormal blue granules of iron deposition within hepatocytes and Kupffer cells



Iron Overload Cardiomyopathy

Primary Hemochromatosis

Type 1: HFE
Type 2: Hemojuvelin
Type 3: Transferrin
Type 4: Ferroportin

Secondary Iron Overload

1. Hemoglobinopathies
2. Blood Transfusions
3. Myelodysplastic/fibrotic
4. Aplastic anemia
5. IV iron supplementation
6. Friedrich's ataxia
7. Chronic liver disease

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Gulati, V et al. *Cardiology in Review* 2014;22: 56–68

Patient Case #2

- 45 year old Caucasian male found to have borderline diabetes and thrombocytopenia on routine physical exam
  - Additional evaluation….liver ultrasound that showed cirrhosis
  - No history of alcohol
  - Ferritin 2200
  - Liver biopsy → iron overload
- Family Hx: Sister with liver disease
- Found to have C282Y homozygosity for the HFE gene

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Patient Case #2

- Treatment for Primary Hemochromatosis
  - Weekly phlebotomies

- Subsequent clinical course
  - Development of Type II Diabetes
  - Atrial Fibrillation
  - Congestive heart failure

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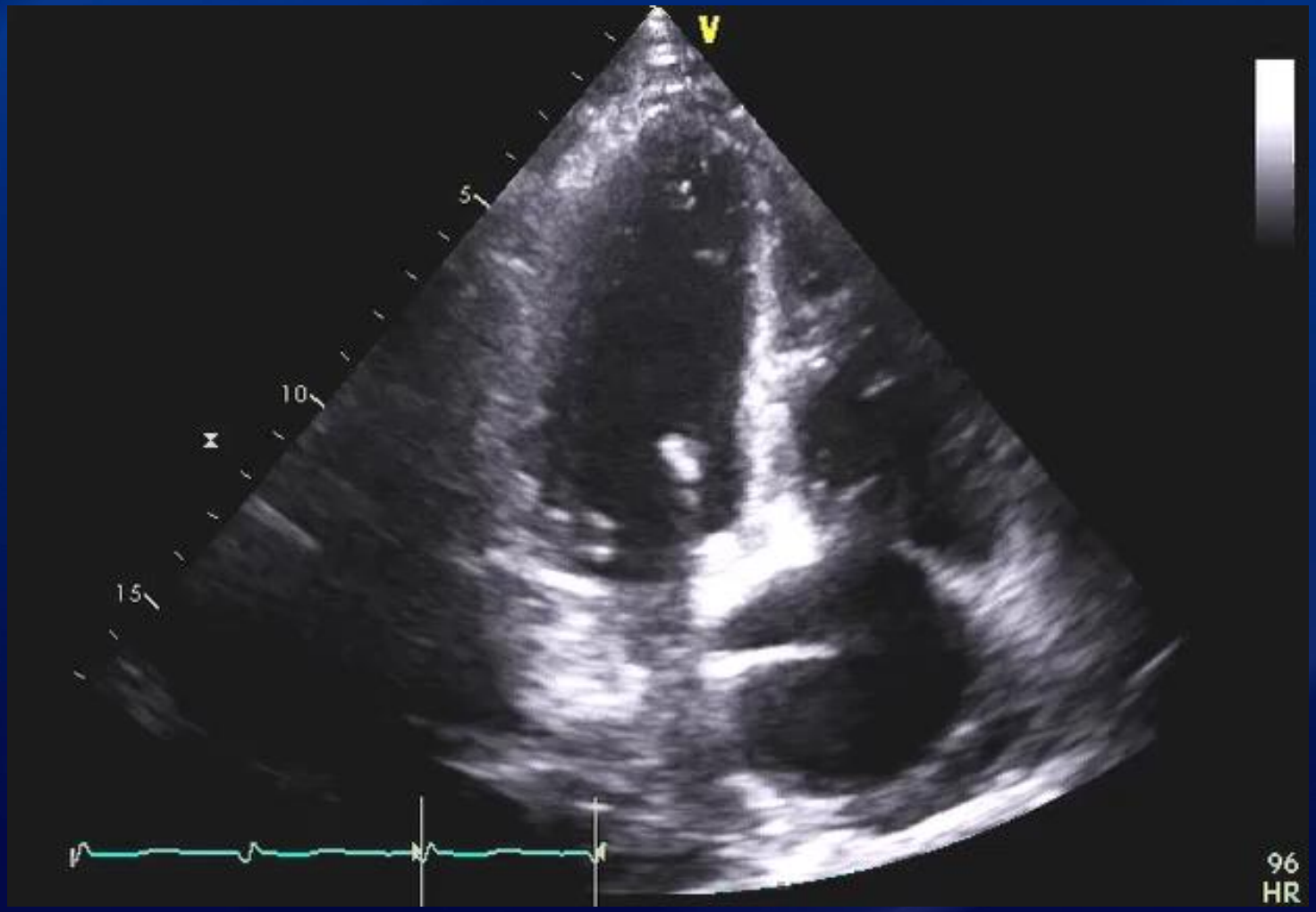

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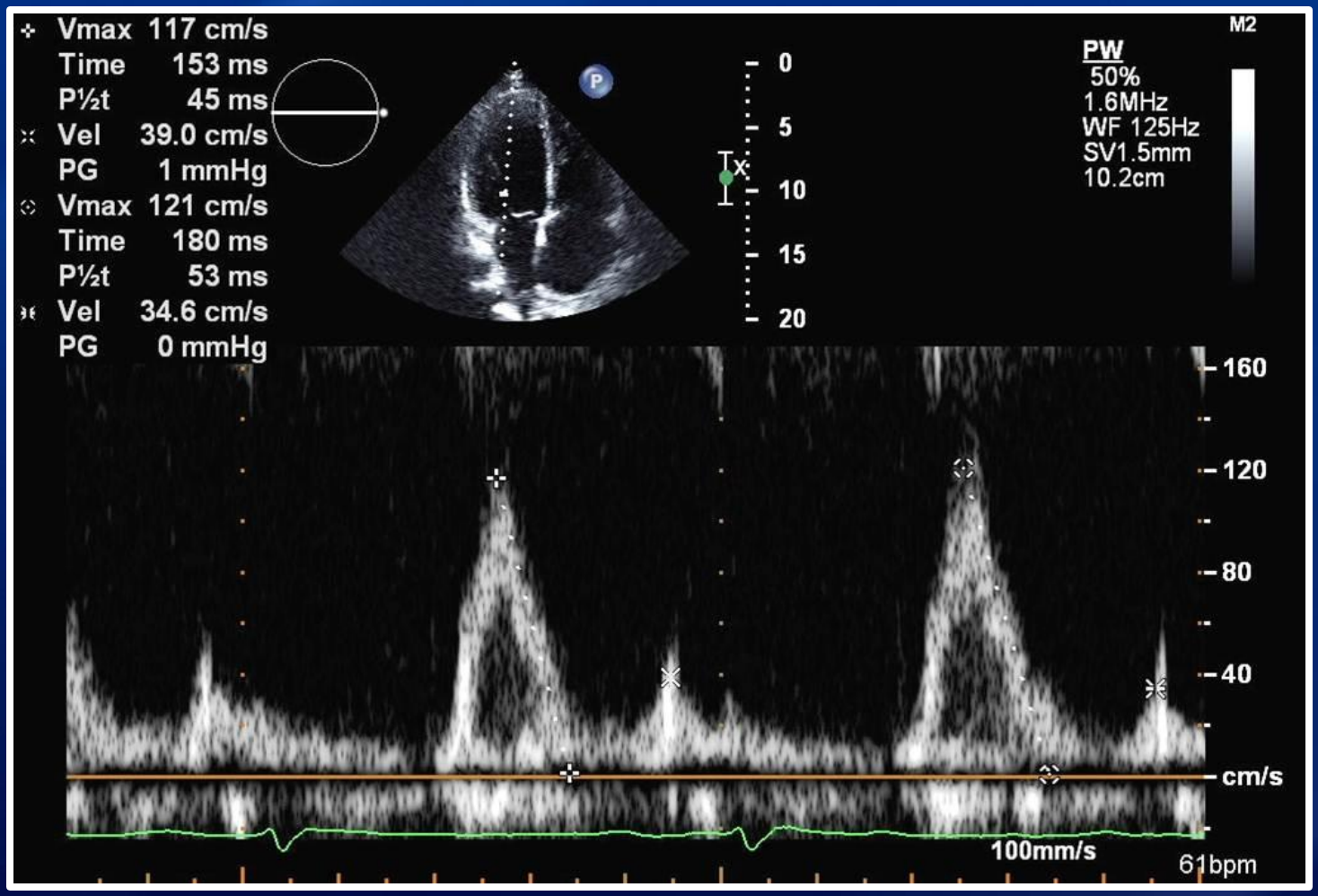

E/A ratio = 3.67

Grade III diastolic dysfunction with increased LA pressure

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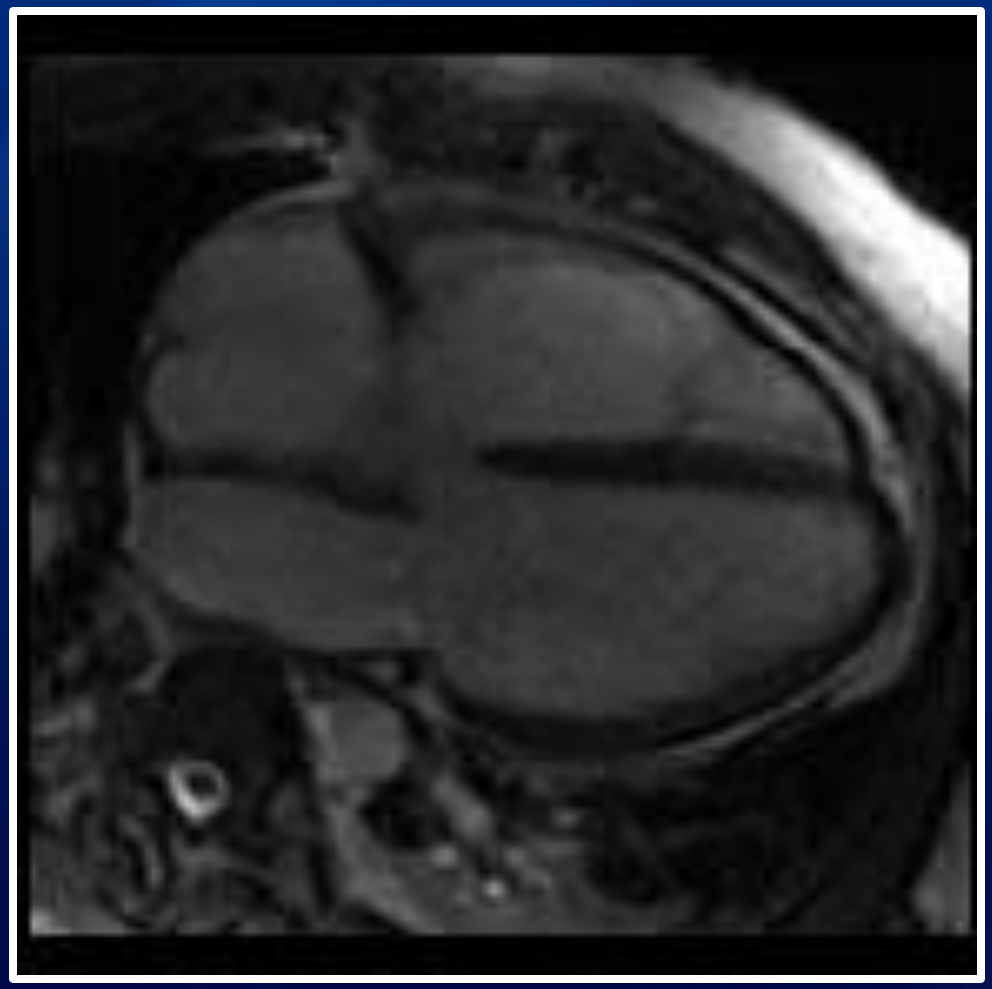

EF 44%
LV enlargement
RV enlargement
Biatrial enlargement

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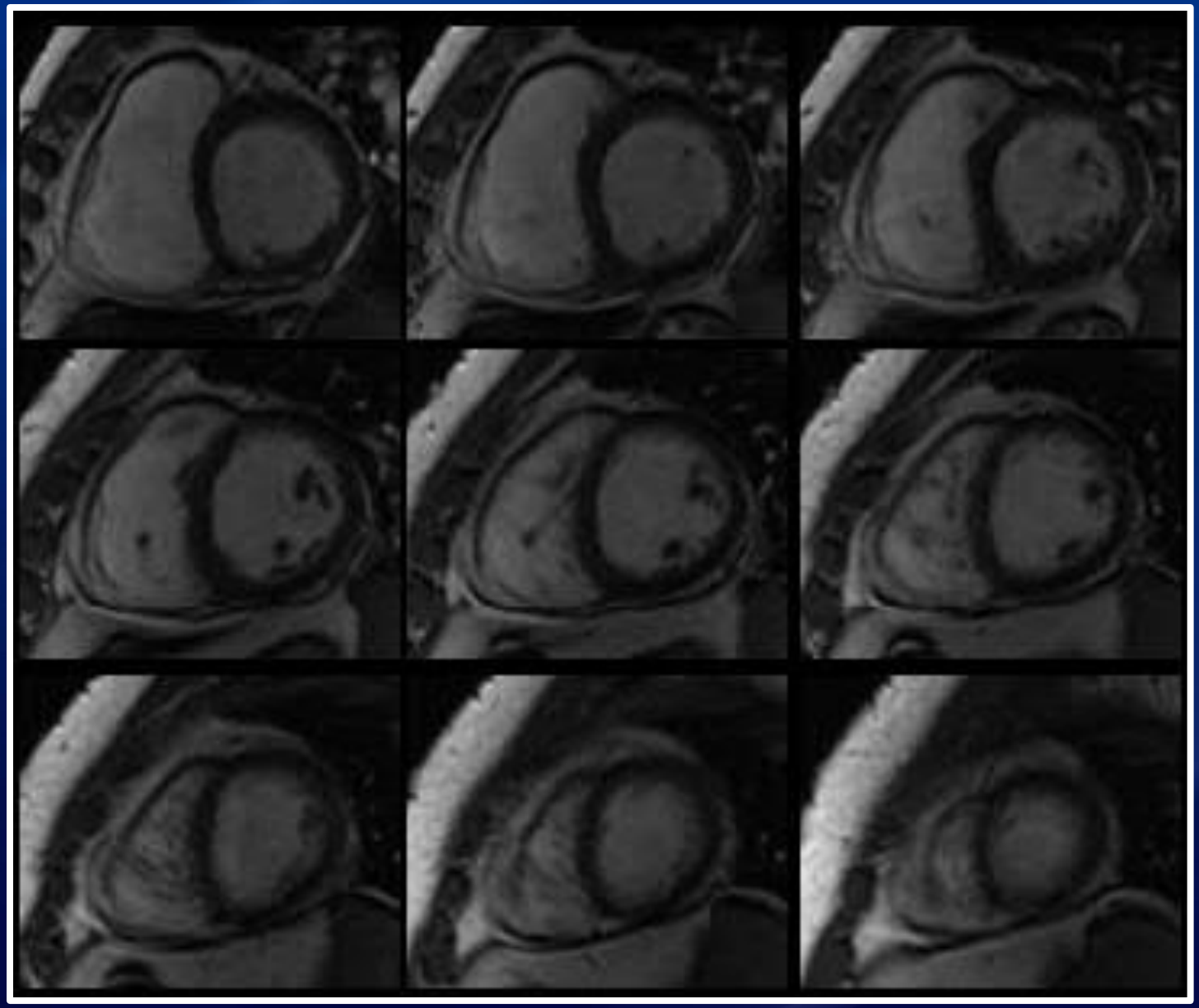

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Question #2

In order to determine if cardiac iron deposition is the cause of the patient's congestive heart failure, the best MRI technique to use is?

- A. T2 mapping
- B. T2* decay time
- C. Visual estimate of myocardial iron deposits
- D. Late gadolinium enhancement

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Relaxation Time

- Time to “relax” excited signals coming from protons in the body exposed to a MRI
- Iron overloaded hearts, paramagnetic effect shortens the relaxation time
- MRI can use small magnetic fields (***gradient echo***) at specific time intervals (***echo time*** = TE) to refocus the relaxation signals
- Measure the signal decay time (relaxation time) = T2*

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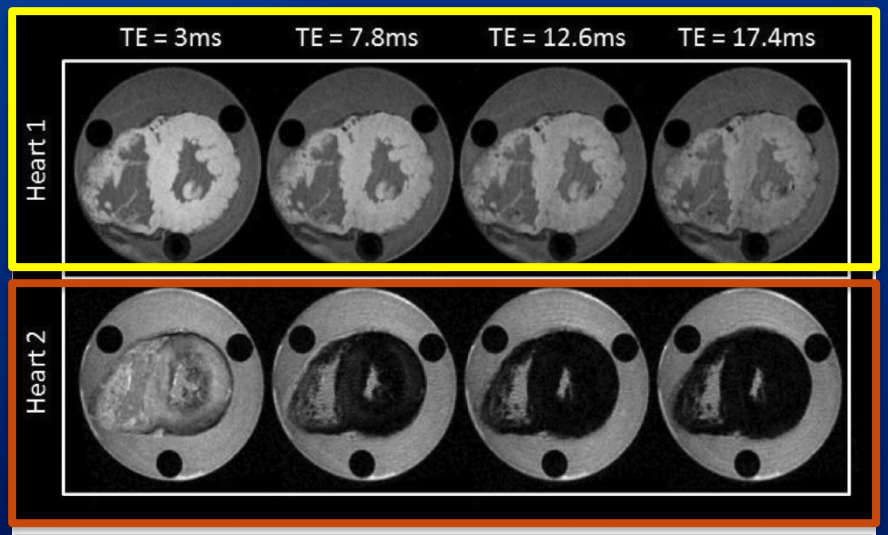
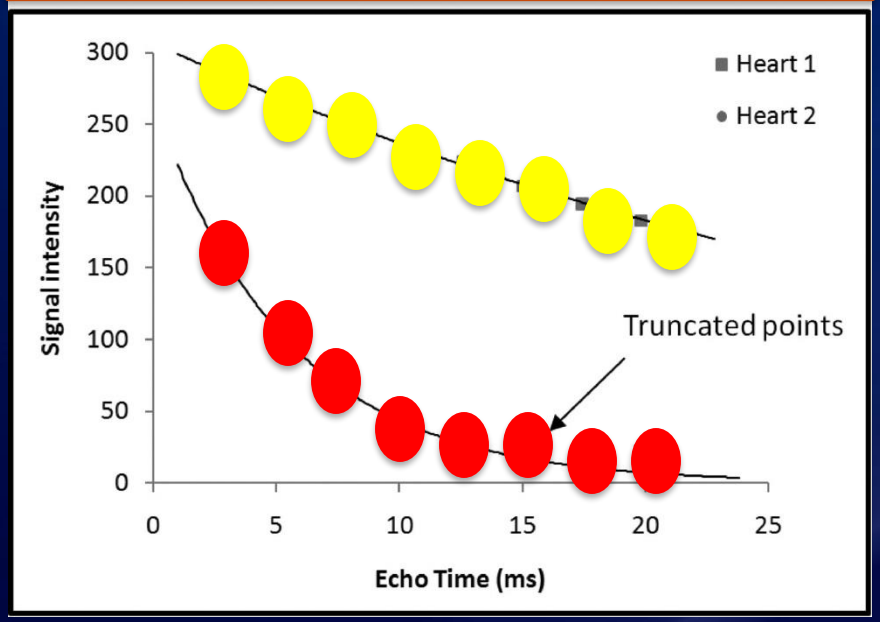
Gujja P, et al. JACC 2010;56(13):1001-1012

Example of ex vivo cardiac T2* scans.

Normal

Iron Overload





Normal
T2* > 20 msec

Iron Overload
T2* < 10 msec

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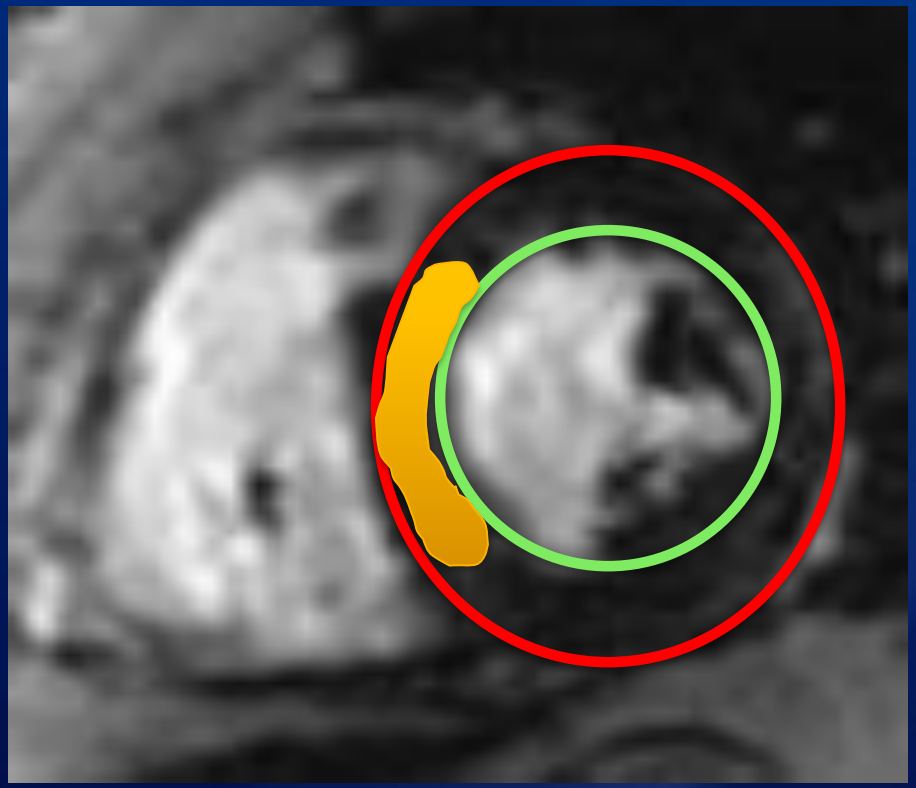
American Heart Association.

Carpenter J et al. Circulation. 2011;123:1519-1528

Measuring T2*

- Gradient Echo images
- Short axis stack
- Transmural ROI
- Interventricular septum
- Susceptibility artifacts from cardiac veins and lungs limit other regions
- Decay curve → T2*



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Question #3

What value for T2* predicts the greatest risk for congestive heart failure due to cardiac iron deposition?

- A. <10 msec
- B. 10-20 msec
- C. >20 msec

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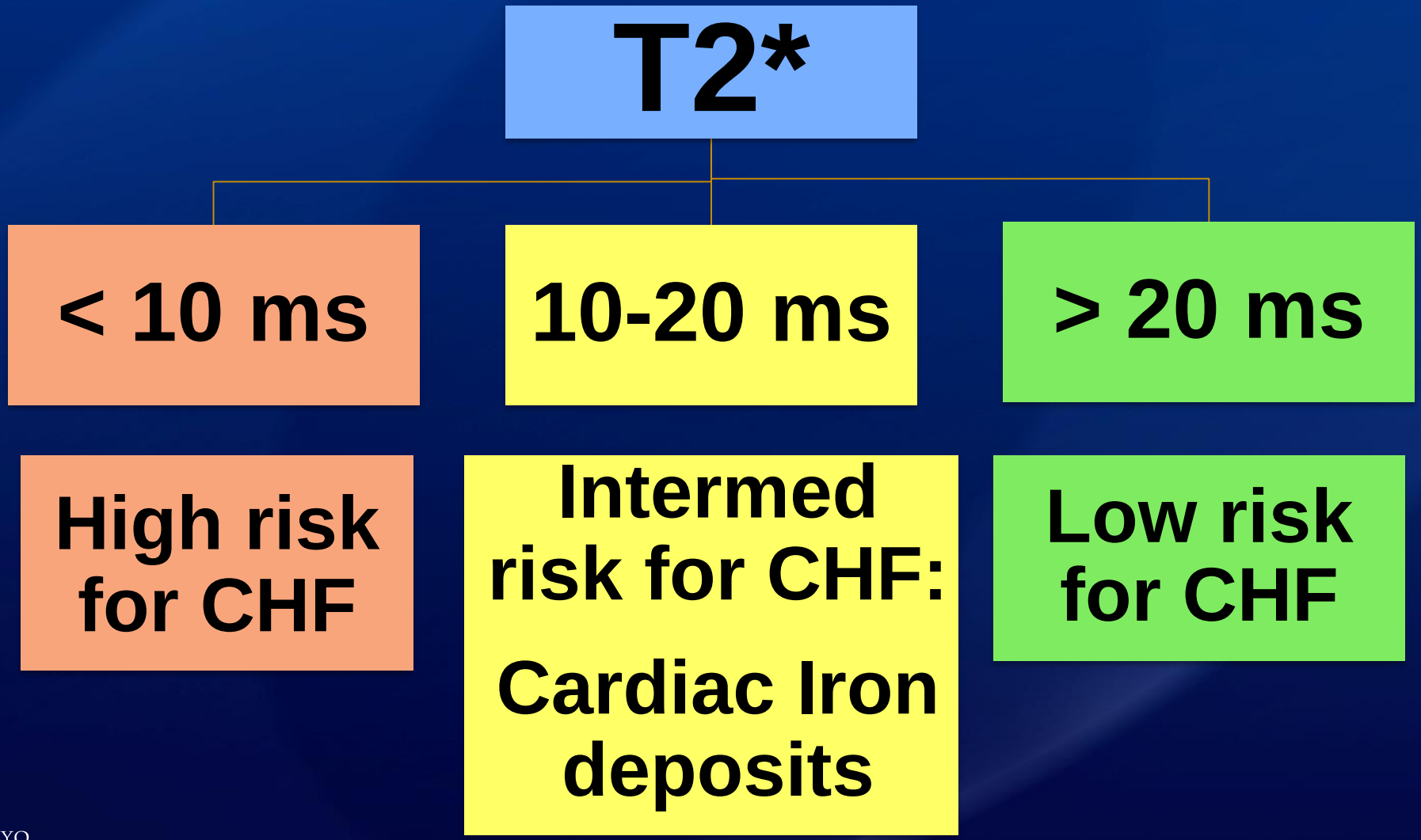
T2* → Diagnosis of Cardiac Iron Deposits and Predicts CHF Risk



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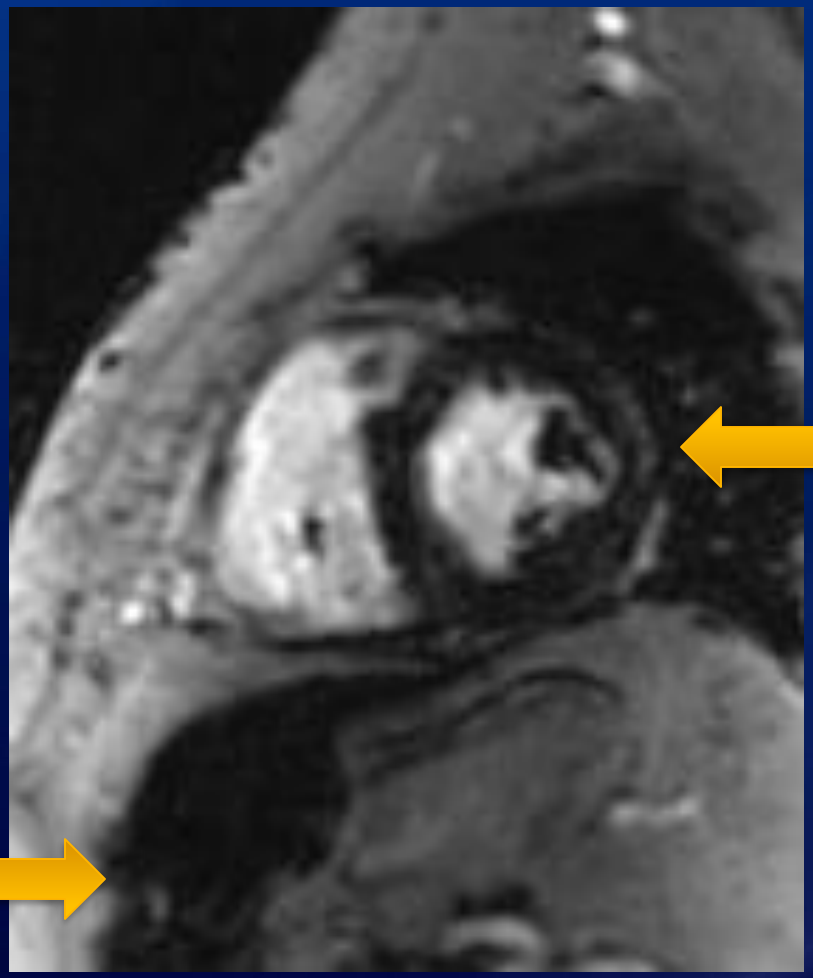
Gujja P, et al. *JACC*. 2010;56(13):1001-1012
Wood, JC. *Curr Opin Hematol*. 14 2007:183-190

Patient Case #1



T2* = 12 ms
Cardiac iron

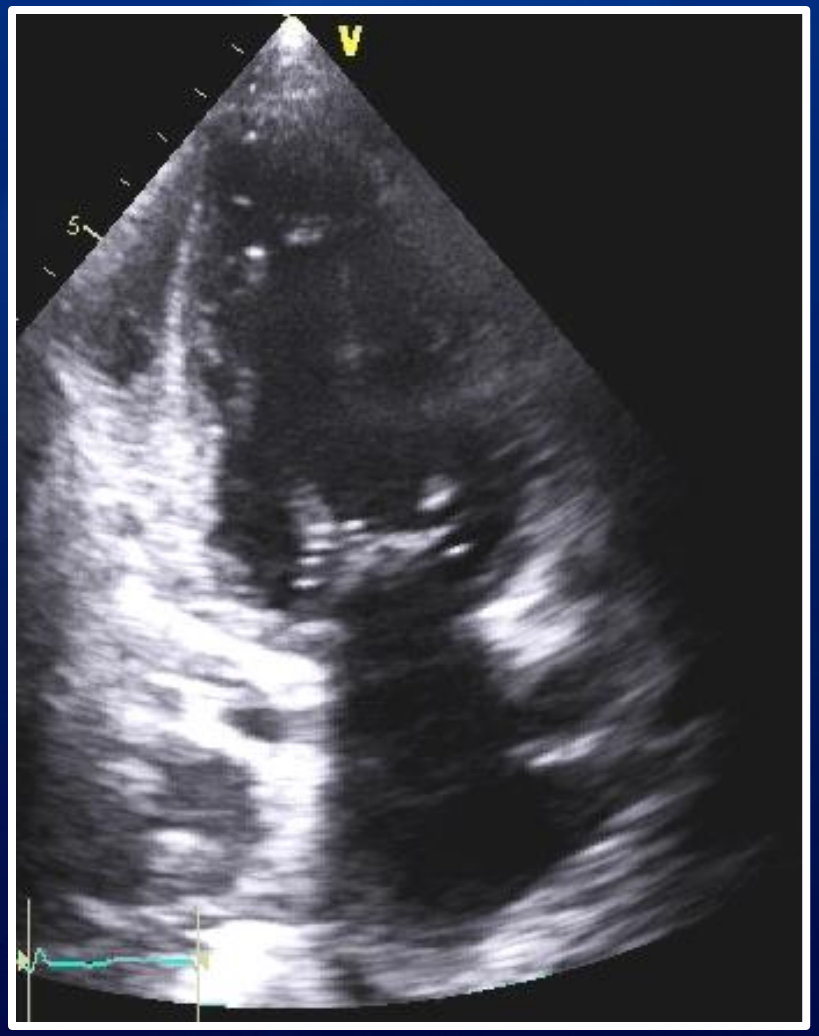
Hepatic iron

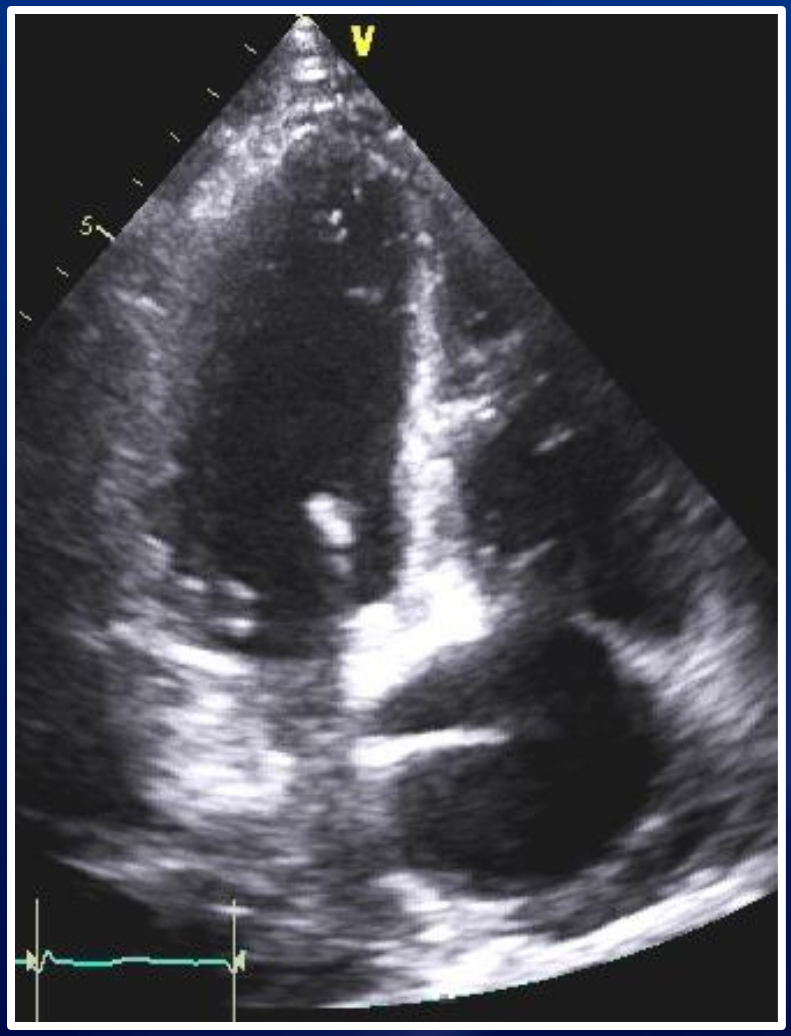
Patient Case #3

- 43 year old woman with homozygous sickle cell disease with chronic transfusions
  - Recurrent acute chest syndromes
  - Ferritin 8,421
  - Hemoglobin 8.5
  - Hematocrit 25.9

Patient Case #3

- Cardiac involvement
  - Chronic diastolic heart failure (EF 55%)
    - RHC: PCWP 22mmHg
  - Atrial fibrillation
  - Edema





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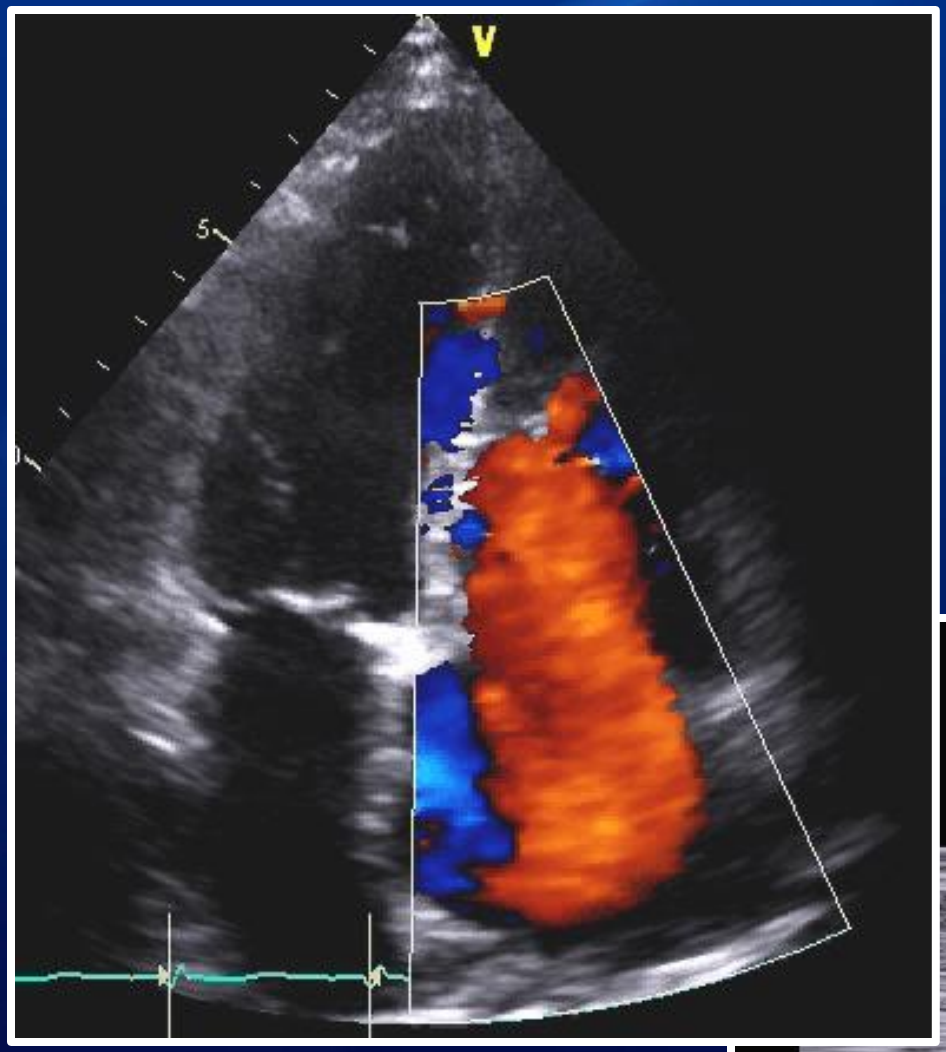

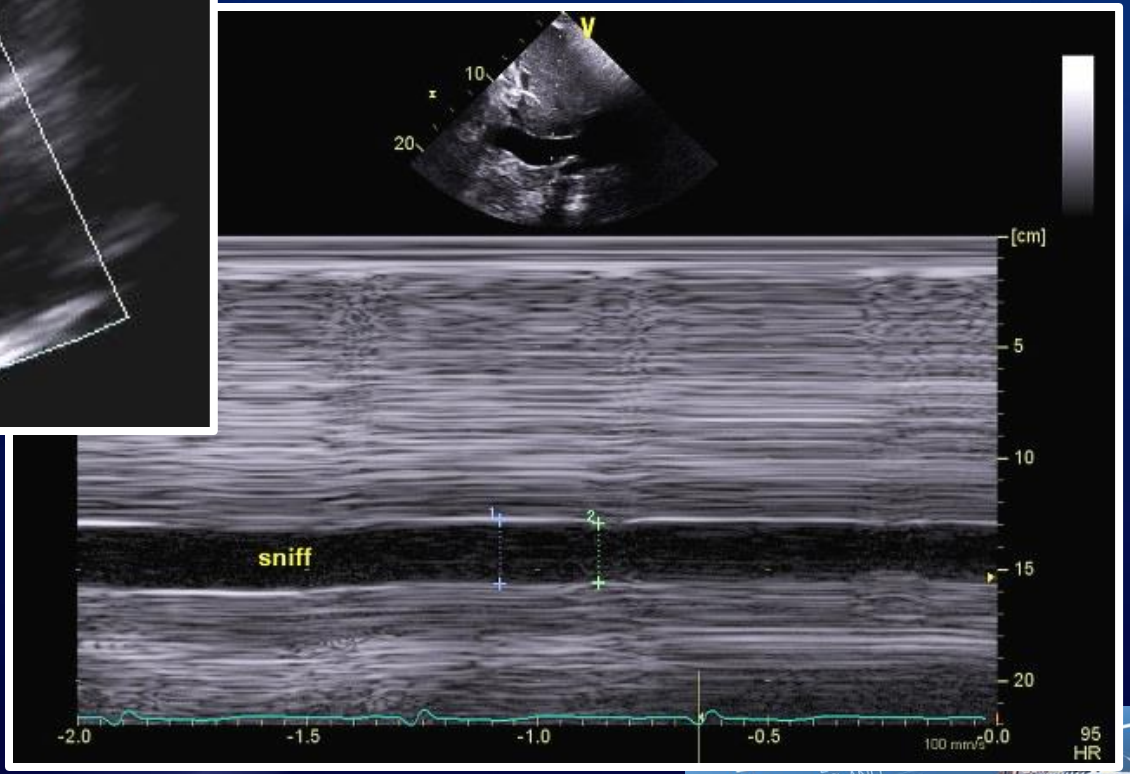

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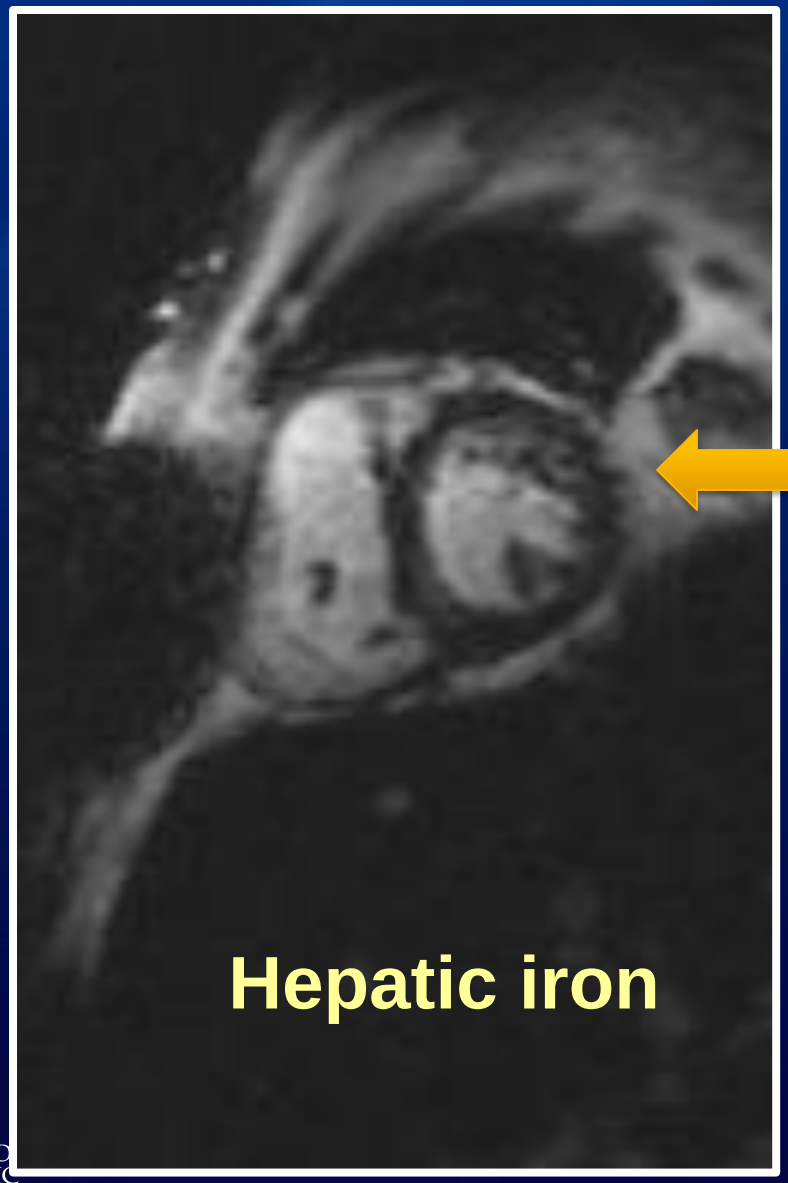

T2* = 9 ms

Cardiac iron

T2* Analysis

Non Linear Fit/Truncation

Slice 1

Freehand ROI 1

T2* = 9.2 ± 0.53 ms R^2=0.987

Non Linear Fit/Truncation

Slice 2

Freehand ROI 1

T2* = 8.1 ± 1.06 ms R^2=0.936

Non Linear Fit/Truncation

Slice 3

Freehand ROI 1

T2* = 8.4 ± 1.88 ms R^2=0.807

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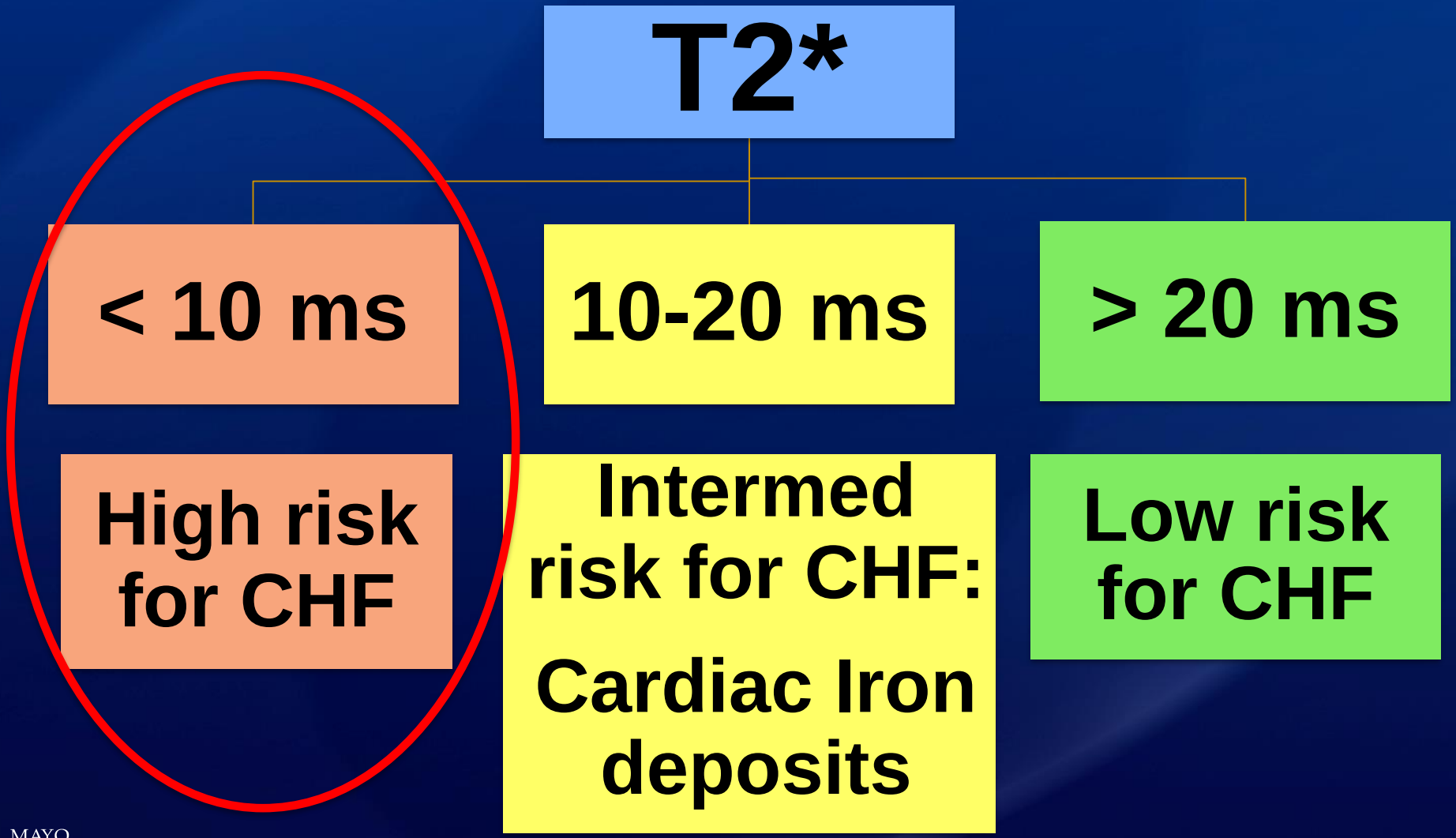
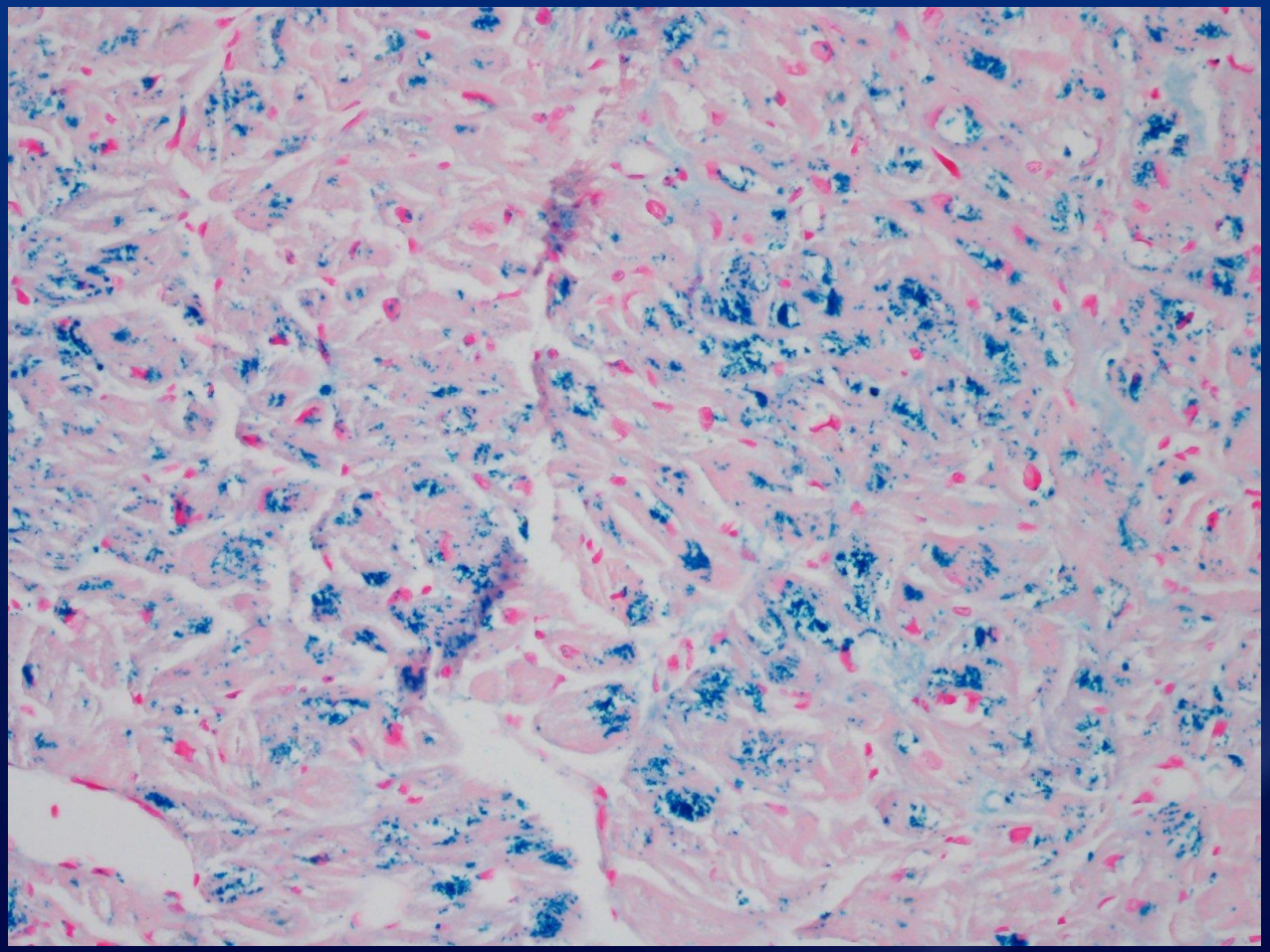
CMR in Iron Overload Cardiomyopathy



Gujja P, et al. *JACC*. 2010;56(13):1001-1012
Wood, JC. *Curr Opin Hematol*. 14 2007:183-190

Endomyocardial Biopsy
Prussian Blue Stain for Iron



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Practical Approach:
Evaluation for Iron Overload Cardiomyopathy

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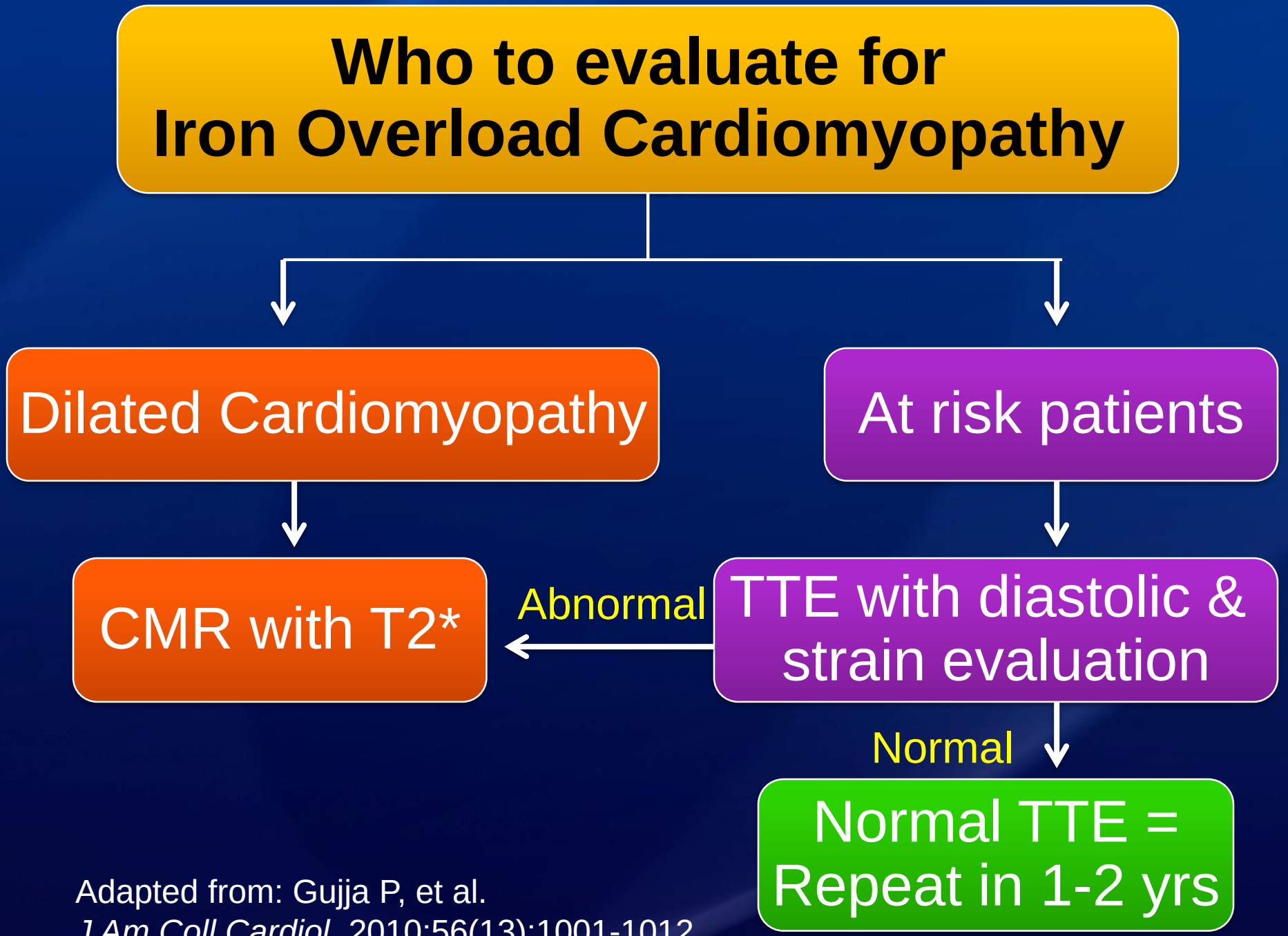
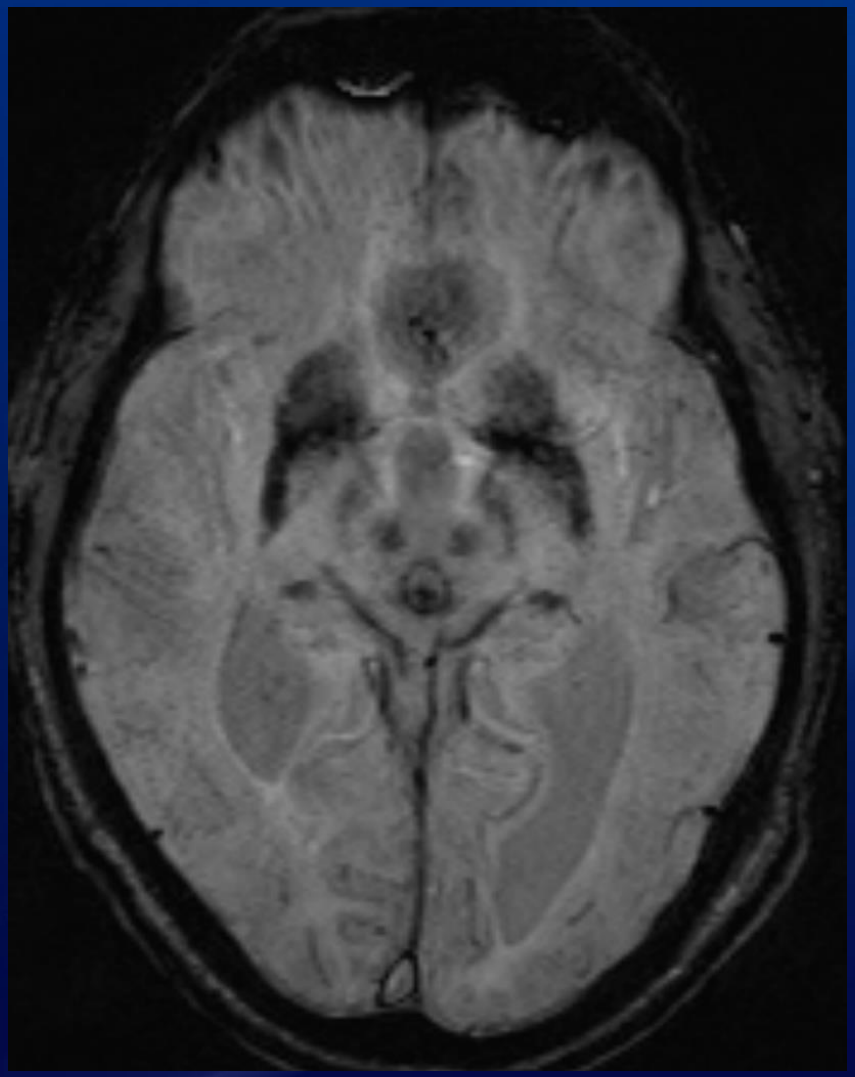


Adapted from: Gujja P, et al.
J Am Coll Cardiol. 2010;56(13):1001-1012.

Other organ systems to consider: CNS Iron Deposition

- 45 yo male with h/o hereditary hemochromatosis and cirrhosis
- MRI revealed local loss of SI from iron deposition in the brain, including the dentate nuclei, basal ganglia, and putamen



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Rosana A, La Rosa L. Blood Transfus. 2007 Nov; 5(4): 241–243.

Take Home Points

- Hemochromatosis and other iron overload states can lead to multisystem failure, most notably hepatic and cardiac disease
  - Cirrhosis and portal hypertension
  - Diastolic dysfunction
  - Dilated cardiomyopathy
  - Arrhythmias

- T2* reflects hepatic or cardiac iron stores and can predict the development of congestive heart failure
  - <10 msec = High risk
  - 10-20 msec = Intermediate risk
  - > 20 msec = Low risk

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Conclusion:

MR imaging provides assessment of multi-system iron deposition, particularly in the heart and liver. This enables non-invasive quantification of iron content in patients with abnormal iron deposition, obviating the need for invasive assessment, and providing guidelines for intervention and determination of prognosis.

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Thank you!

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