How I do Thalassaemia.

Mark Westwood.

The Heart Hospital,

London,

UK.

Important disclaimer: Although the use of T2* is described in detail here no responsibility can be taken for the accuracy of any T2*measurements made with the use of this document or any clinical decisions taken as a result.

Introduction:

LV dysfunction due to iatrogenic cardiac iron overload from transfusions remains the commonest cause of death in developed countries in patients with thalassaemia major. Despite being treatable and reversible if adequate intensive iron chelation therapy is started in time approximately 50% of patients with thalassaemia major die before reaching 35 years of age. The problem with early detection of myocardial iron loading is that symptoms occur late in the progression of the disease. Similarly, parameters of ventricular function do not change until considerable iron deposition has occurred. T2* can assess tissue iron concentrations over a large range including mild and moderate degrees of iron loading. This therefore allows early treatment before symptoms develop which is important as once symptoms of heart failure develop there is a considerable mortality even with the use of intensive chelation. As there is no clinical useful correlation between either serum ferritin or liver iron concentrations and myocardial iron loading T2* provides a unique method for the accurate, reliable and reproducible assessment of myocardial iron concentration. Recent published work using this technique to guide appropriate chelation strategies has been highly encouraging and has further demonstrated the power and clinical utility of this technique.

GE, Siemens and Philips have sequences available for assessment of myocardial iron loading.

Overview:

1) Patient preparation.
2) Pilot Images.
3) Setting up the myocardial T2* acquisition.
4) Setting up the hepatic T2* acquisition.
5) Analysing the myocardial T2*.
6) Analysing the hepatic T2*.
7) Limitations of the technique and special considerations.
8) Validation and calibration

1) Patient preparation.

Standard precautions as for any patient are to be applied. However, special care should be taken to remove all infusion pumps. Baxter® infusion pumps or other similar devices containing iron cheating agents should also be removed as they can interfere with T2* image acquisition and subsequent analysis. If a radio transmitting ECG device is used for gating the part that transmits the ECG signal should be placed as far away from the heart and liver as possible.

2) Pilot images/volumetric analysis.

After standard pilot images, long axis cine images (2ch and 4ch) should be acquired – see ' How I do a CMR volume study. A short axis cine stack for volumetric analysis should also be acquired. It is important to remember that due to the effects of the chronic anaemia the standard adult normal ranges for volumetric analysis do not apply and that a different set of values should be used (see pubmed JMRI 2007).

3) Setting up the myocardial T2* acquisition.

This is described for a single breathold multiecho acquisition for which there is the most published data. Position the slice as a short axis slice in the ventricle mid way between the base and the apex (figure 1). Image acquisition should be set to occur immediately after the R wave. At least for one manufacturer, it is important not to alter any settings that may change TE (eg FOV), or T2* derivations may be inaccurate.

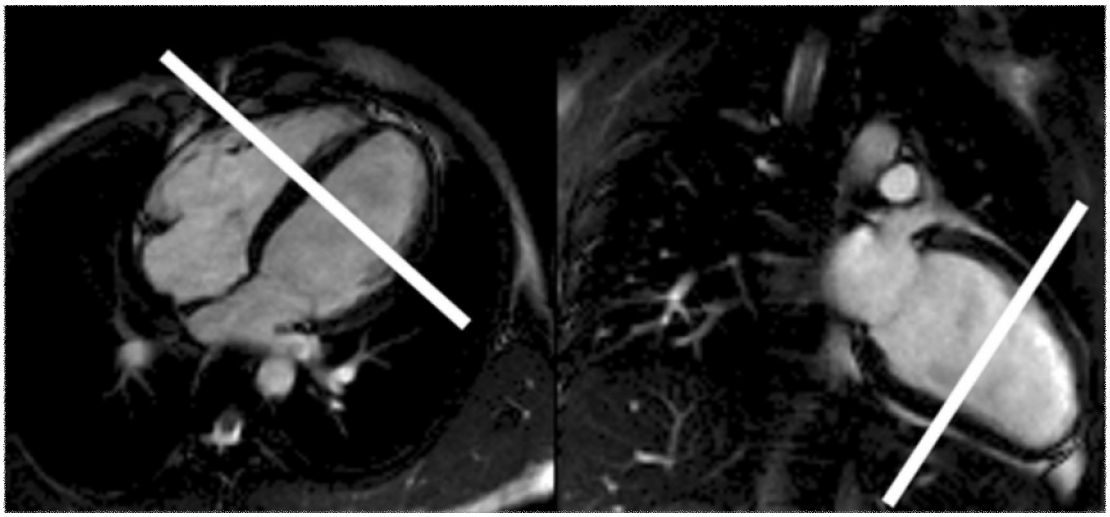


Figure 1: The slice position for the myocardial T2*acquisition is shown by the thick white line on the two and four chamber images.

4) Setting up the hepatic T2* acquisition.

Position the slice as a transverse slice across the liver 4cm below the dome of the diaphragm as shown in figure 2.

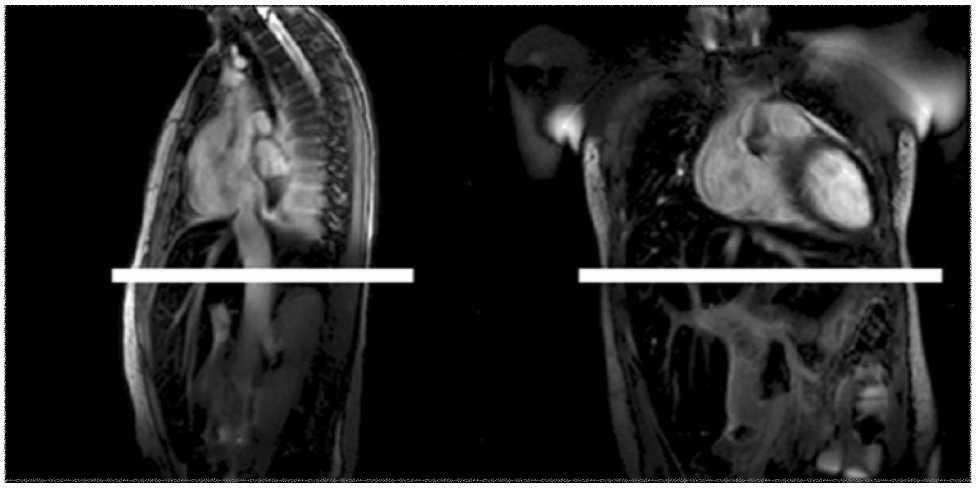


Figure 2: The slice position for the hepatic T2* acquisition is shown by the thick white line on the coronal and sagital pilot images.

5) Analysing the myocardial T2*

Draw a region of interest in the myocardial septum encompassing both the endocardial and epicardial borders (as there is more iron in the epicardium and endocardium) but away from the right ventricular insertion points (figure 3). The same region of interest should be copied to each of the images with different TE's (figure 4). The signal intensity in each region should then be obtained. Most analysis packages (such as Argus, CMRtools) will calculate average signal intensity for a given region. A graph of signal intensity vs echo time can then be plotted using a spreadsheet such as Excel (figure 5). The best fitting exponential decay curve with the formula $SI=ke^{-(TE/T2^*)}$ should be drawn. It is important to exclude points where the signal intensity is very low (as occurs with severe iron loading shown in figure 5 by the points circled). As a guide, if the recorded signal intensity is not at least double the background signal intensity then this point should be excluded from the curve fitting.

All work to date demonstrates that myocardial T2* values of greater than 20ms are normal (figure 6) and those below 20ms indicate iron loading. As the myocardial T2* decreases further the myocardial iron loading increases and alterations to chelation therapy may be needed. Severe iron loading is usually taken as a myocardial T2* of less than 10ms (figure 6). It is important to note that even with very severe myocardial iron loading (such as a T2* of less than 8ms) the LVfunction may be normal. This apparent normal ventricular function does not mean that the patient is not a risk of developing LVimpairment from the iron loading which can occur unexpectedly and rapidly.

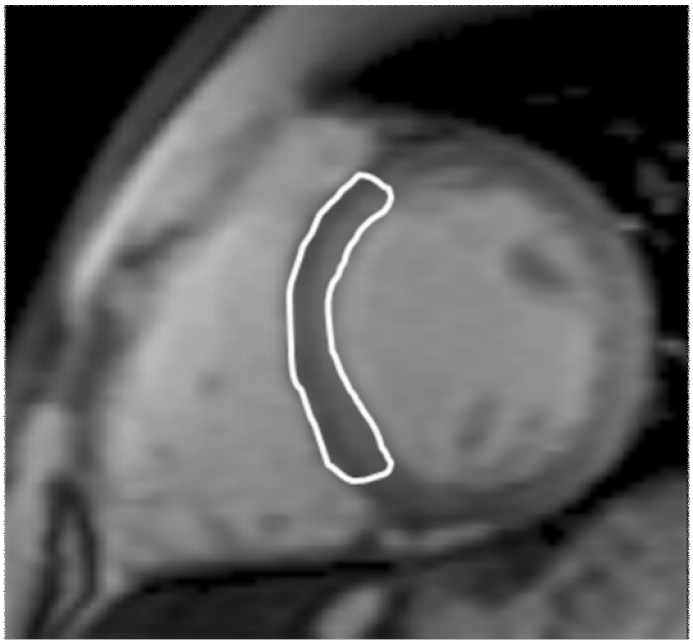


Figure 3: The region of interest for the calculation of the myocardial T2* is shown which clearly encompasses both the endocardial and epicardial borders of the interventricular septum.

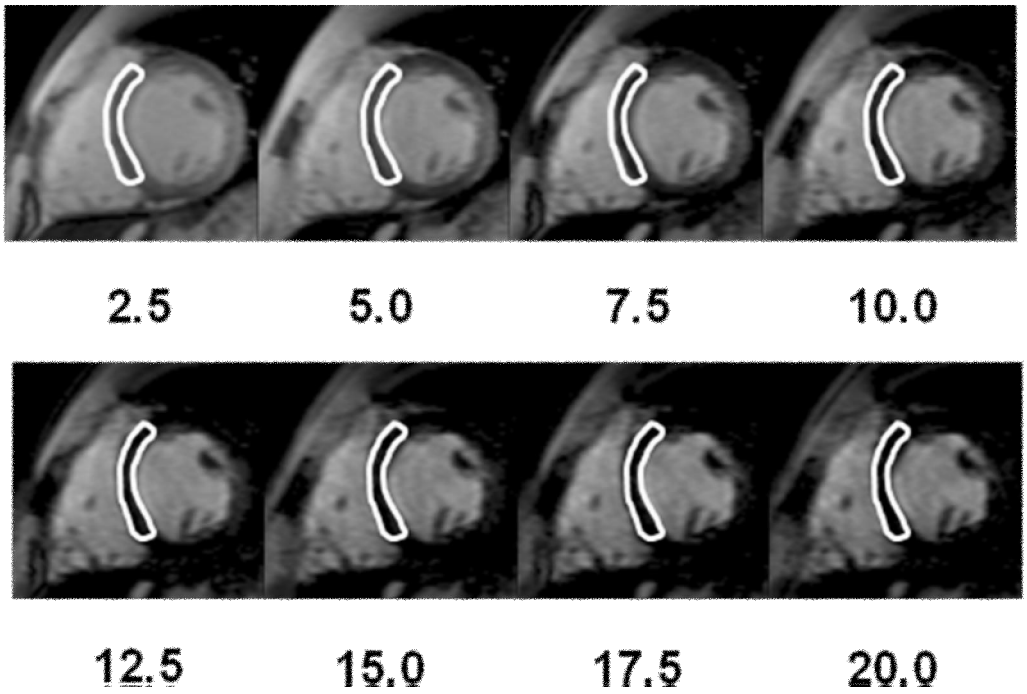


Figure 4: The Region of interest has now been copied to all the acquired images. The echo times of the all the images are shown below each image.

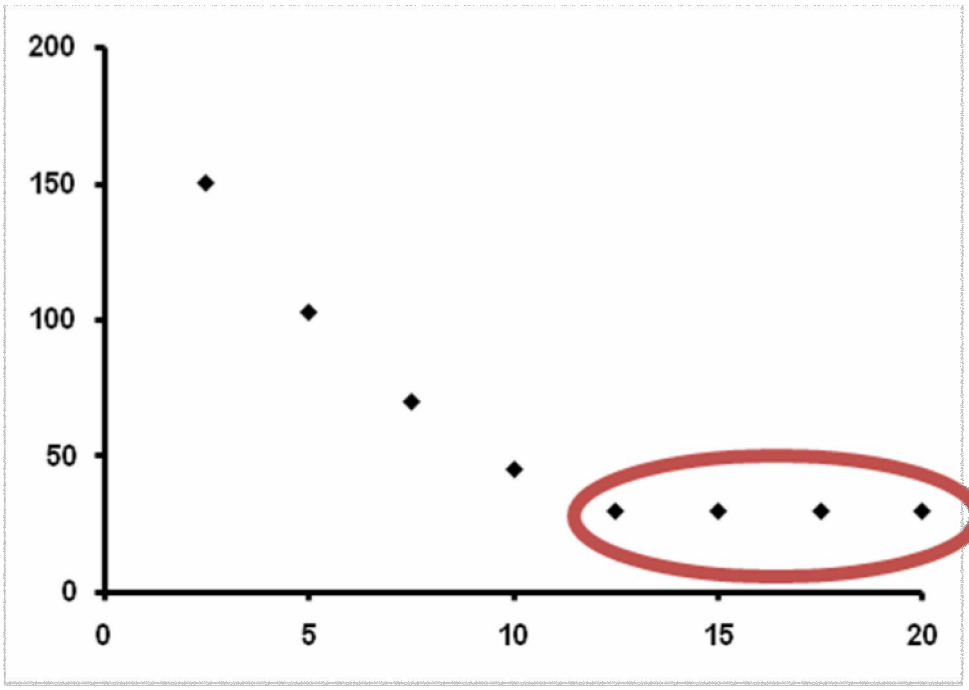
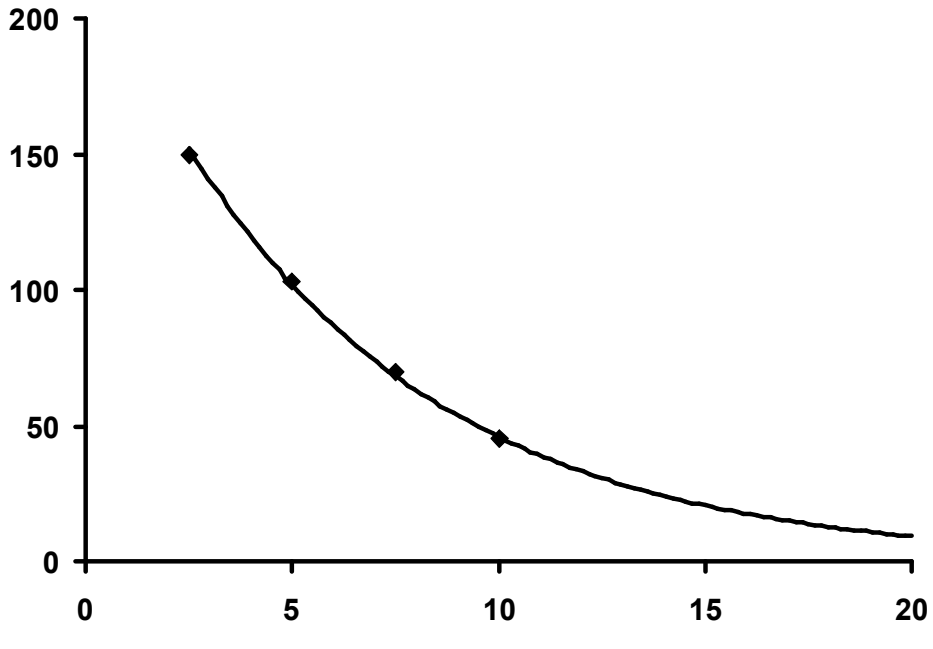


Figure 5: The signal intensity (y axis) has been plotted against echo time (x axis) for each image in the cardiac T2* acquisition. The points circled in red have only background signal intensity and should be excluded when identifying the exponential decay curve of best fit (see below).



F ts with equation $y=226e^{-0.16x}$. From this the T2* in this example is calculated as 1/0.16 which is 6.25ms.

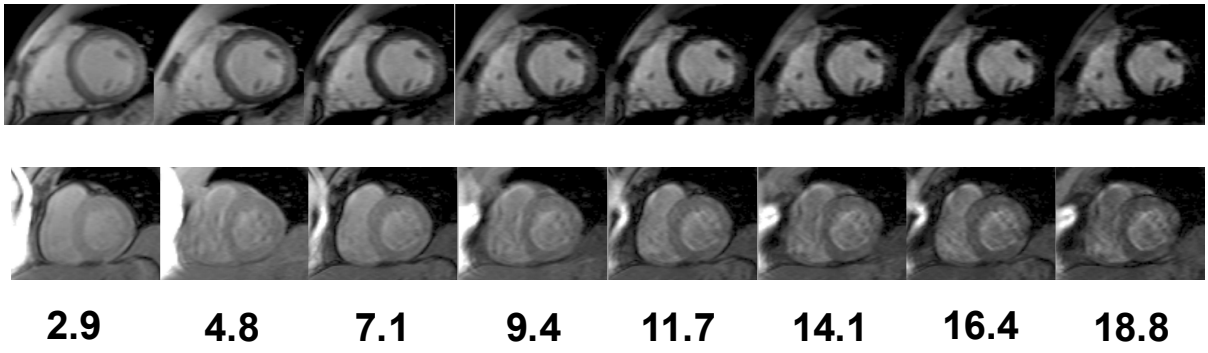


Figure 6: Two series of myocardial T2* acquisitions. The upper series of images demonstrate severe myocardial iron loading with a T2* of 7.5ms. The lower series of images are of a normal heart with a T2* of 32ms.

6) Analysing the hepatic T2*.

Draw a region of interest in the liver away from any of the biliary tree or hepatic veins and arteries (see figure 7). Then continue as above for the heart.

Liver T2* has been calibrated against liver biopsy samples. Based on this a liver T2* of more than 6.3ms equates to less than 2mg/g dry weight of iron present in the liver (which is considered to indicate that all the excess iron in the liver has been removed) and a liver T2* of less than 1.4ms equates to more than 10mg/g dry weight of iron present in the liver (which is considered to be severe hepatic iron loading).

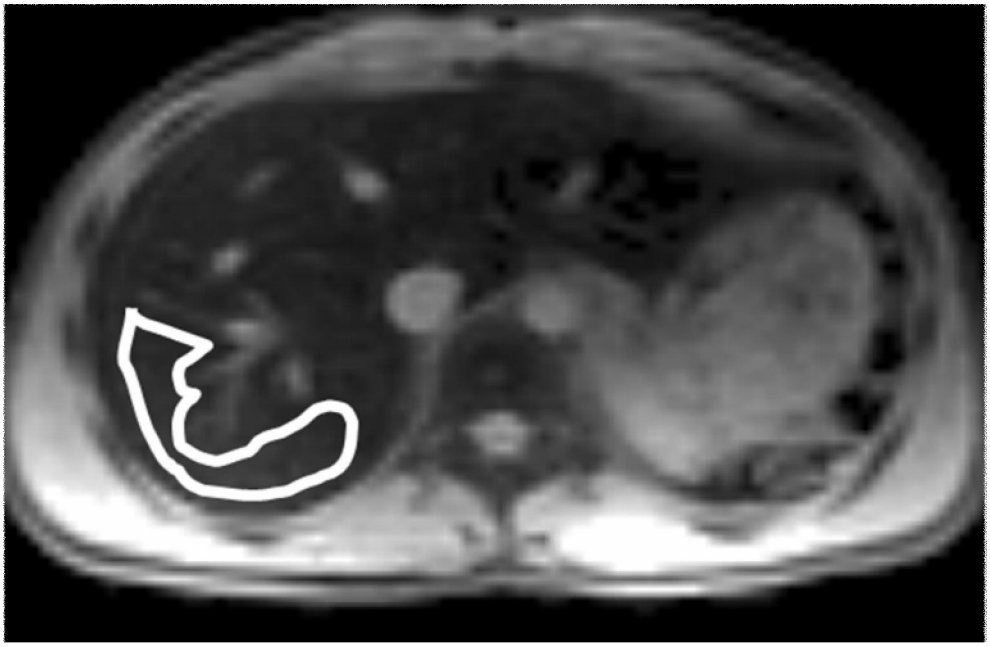


Figure 7: The region of interest drawn for the calculation of the hepatic T2* is shown. A large region is drawn which is clear of the hepatic veins and biliary tree.

7) Limitations of the technique and special considerations.

Often the acquisitions for myocardial T2* are long (especially if using multiecho sequences). This may result in a large amount of artefact across the image (see figure 6) which will then cause inaccuracy of the calculated T2*. This artefact is most pronounced in the images with the highest TE and the image with the greatest TE should also be inspected for the degree of this artefact. The images obtained should have clearly defined blood/myocardial edges that are not blurred particularly at the septum. If there is significant blurring of this border (see figure 7) then the acquisition should be repeated. If images are used that contain a large amount of this artefact then the calculated T2* value will be higher than the actual T2*. This is because the T2* calculated will be a mixture of that for the myocardium and the blood pool in the ventricle.

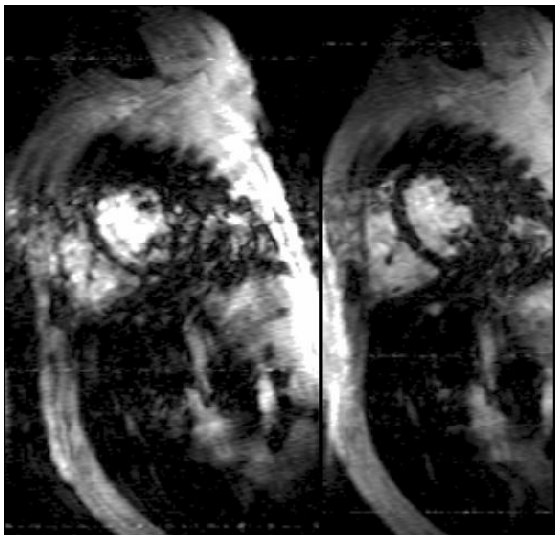


Figure 7: On the image on the left there is a large amount of artefact across the image due to poor breath holding. This then improved with the subsequent image acquisition on the right. Analysis of the image on the left would lead to a calculated T2* higher than the true T2* value. The images shown are with an echo time of 18.8ms.

You should ensure that the acquisition has been fully validated and calibrated. It is also worth noting that myocardial and hepatic iron loading are not correlated as previously thought (see figure 8).

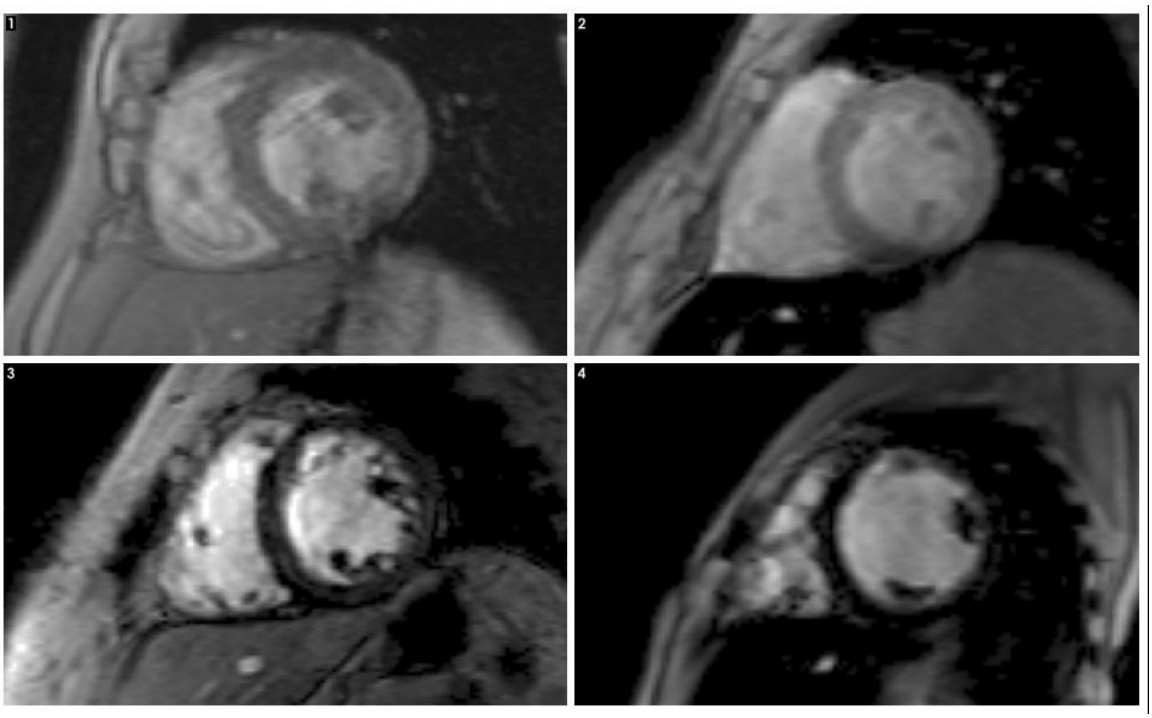


Figure 8: Various iron loading states. Top left: no significant myocardial or hepatic iron loading. Bottom left: both severe myocardial and hepatic iron loading. Dissociated heart/liver iron deposition: solely in the liver (top right) or myocardium (bottom left). All four images have the same echo time of 6.7ms.

8) Validation and calibration.

Assessment of tissue iron concentrations using T2* has been extensively studied and the method has been exhaustively validated and caliubrated. There is growing evidence that there is good Interstudy/interscanner reproducibility, perhaps because the concentration of myocardial/hepatic iron has a very dominant effect on the overall T2* values obtained in these iron overloaded states.

When starting to use T2* expert help should be sought mainly to ensure that the sequence being used has been adequately calibrated and validated.

Further Reading:

Westwood MA, Anderson LJ, Firmin DN, Gatehouse PD, Lorenz CH, Wonke B, Pennell DJ. Interscanner reproducibility of cardiovascular T2* measurements of tissue iron in thalassaemia. JMRI 2003;18:616-620

Westwood M, Anderson LJ, Firmin DN, Gatehouse PD, Charrier CC, Wonke B, Pennell DJ. A single breath-hold multiecho T2* cardiovascular magnetic resonance technique for diagnosis of myocardial iron overload. JMRI 2003;18:33-9.

Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennell DJ. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. EHJ 2001;21:2171–9

Westwood MA, Anderson LJ, Maceira AM, Shah FT, Prescott E, Porter JB, Wonke B, Walker JM, Pennell DJ. Normalized LVvolumes and function in thalassemia major patients with normal myocardial iron. J Magn Reson Imaging 2007; 25: 1147-51.

He T, Gatehouse PD, Kirk P, Tanner MA, Smith GC, Keegan J, Mohiaddin RH, Pennell DJ, Firmin DN. Black-blood T2* technique for myocardial iron measurement in thalassemia. J Magn Reson Imaging 2007; 25: 1205-9.

Wood JC, Tyszka JM, Carson S, Nelson MD, Coates TD. Myocardial iron loading in transfusion-dependent thalassemia and sickle cell disease. Blood 2004; 103: 1934-6.