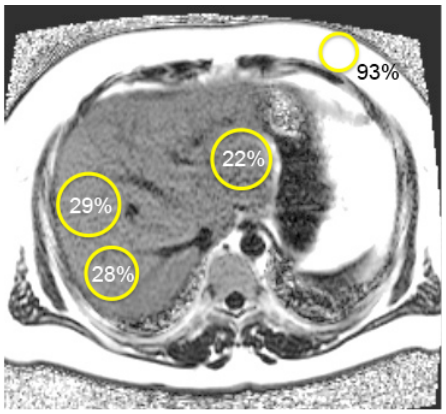
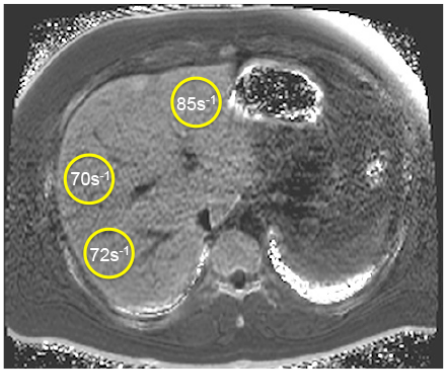
Quick Reference Sheet for Measurement of Liver Fat, Iron and Stiffness



Proton Density Fat-Fraction (PDFF) Map

Figure 1: Measurement of PDFF from PDFF Map. Place several ROI's in representative slices and areas being sure to sample right and left lobes. Report an approximate average or a range if there is marked heterogeneity. Report to the nearest integer. In this case, I would recommend reporting as follows. "Proton density fat-fraction is markedly elevated, ranging from approximately 22-29% (normal < 6%)".



R2* Map

Figure 2: Measurement of R2* from R2* Map. Place several ROI's in representative slices and areas being sure to sample right and left lobes. Avoid ROI's close to the lung bases, stomach or colon. Report an approximate average or a range if there is marked heterogeneity. Report to the nearest integer. In this case, I would recommend reporting as follows. "This study was performed at 1.5T. R2* is mildly elevated, ranging from approximately 70-85 1/s (normal < 60 1/s at 1.5T and < 120 1/s at 3.0T)".

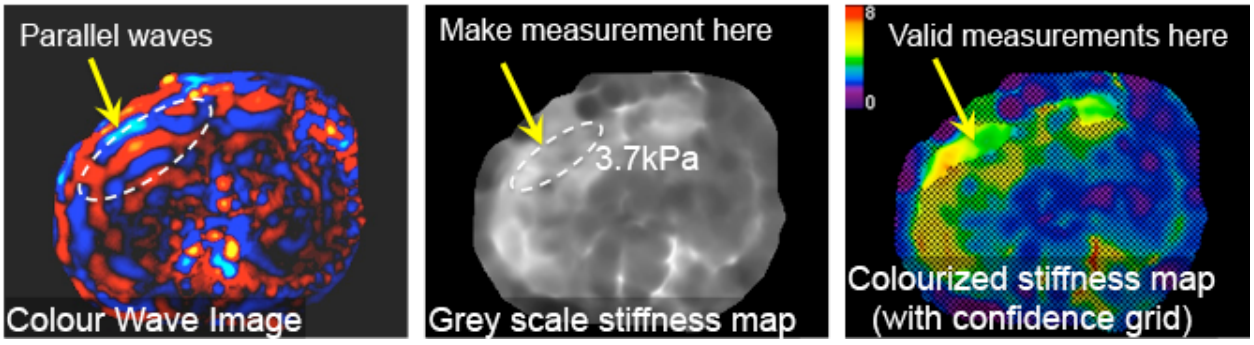


Figure 3: MRE wave images (left) are used to identify high amplitude, parallel waves. Using that region, choose an ROI in the grey scale stiffness map. The colour map with confidence grid can also be used to help select a ROI. Report the stiffness to the nearest 1/10th of a kPa. For suggestions on dictating the MRE results, it will depend on whether the patient has hepatitis C or other causes of diffuse liver disease (eg. NAFLD/NASH). See below for details.

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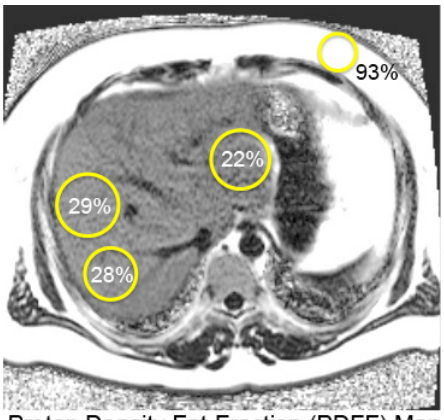
4/16/2019

Practical Issues for Measurement of Liver Fat, Iron and Stiffness with MRI

The following guide is provided to assist with measurement and reporting of liver fat and iron concentrations using IDEAL-IQ, and liver stiffness using MR elastography. Importantly, we are now performing IDEAL-IQ at both 1.5T and 3.0T. Liver fat and stiffness measurements are unaffected by field strength. However, there are important differences in the evaluation of iron concentration between 1.5T and 3.0T. Interpretation and reporting of R2* measurements must be adjusted appropriately (see below).

1. **Liver Fat:** Quantification of hepatic steatosis is made using "IDEAL-IQ", which is now product on most of our scanner systems. The "FF" map provided by IDEAL-IQ, is a parametric map of the proton density fat-fraction (PDFF), which is a fundamental property of tissue reflecting the underlying concentration of triglyceride concentration in the liver. Details of PDFF are discussed at length in the following article: Reeder SB**,** Hu HH, Sirlin CB. J Magn Reson Imaging. 2012 Nov; 36(5):1011-4.
    a. **Measurement of PDFF from ROI's:** the optimal method to measure PDFF from regions of interest has not been rigorously evaluated. The most rigorous evaluations have measured ROI's in all 9 Couinaud segments. Each ROI should be relatively large, with a minimum radius of ~2cm, ideally larger, while avoiding large vessels, dilated bile ducts, or obvious image artifacts. If the study is a follow-up to prior studies, then direct comparison of ROI's from the same location should be made. The value of the measurement is PDFF, in %. A good reference is the subcutaneous adipose tissue which should be approximately 93-95% PDFF.
    b. **Reporting:** My recommendation is to measure 2-4 ROI's in representative regions, including the right and left lobes. Based on these measurements an approximate average value (eg. 13%) or a range of values (eg. 10-15%) that reflects heterogeneity can be reported. The test-retest variability of PDFF measurements is approximately 1% (95% CI) when results from multiple ROI's are averaged. For this reason, report PDFF to the nearest integer, eg. 13%, not 13.1%. The normal value for PDFF is not fully understood, but generally accepted to be normal if less than 6%. ***Suggested dictation***: "Based on measurements in multiple regions of interest, the proton density fat-fraction (PDFF) of the liver is approximately [ ]% (or ranges from [ ] – [ ]%), which is normal/abnormal (normal < 6%)." Please also comment if there are any changes from prior studies, as well as other features such as marked heterogeneity of the fat, etc.
    c. **Pitfalls:** There are three main pitfalls to be aware of. First, any significant motion or ghosting artifacts can corrupt PDFF measurements. I would also avoid measurements in blood vessels, which can have flow related artifacts that are not readily obvious. Second, water-fat swapping occasionally occurs, particularly at the dome of the liver. These values are not valid. Please note that in the area of swap, this is not a simple water-fraction and one should not attempt to calculated PDFF as 100% – water-fraction. Finally, in patients with severe iron overload (~R2*>300-400s^{-1} at 1.5T or R2*>600-700s^{-1} at 3.0T) the PDFF value may not be valid.



Proton Density Fat-Fraction (PDFF) Map

Figure 1: Measurement of PDFF from PDFF Map. Place several ROI's in representative slices and areas being sure to sample right and left lobes. Report an approximate average or a range if there is marked heterogeneity. Report to the nearest integer. In this case, I would recommend reporting as follows. "Proton density fat-fraction is markedly elevated, ranging from approximately 22-29% (normal < 6%)".

2. **Iron Overload:** Quantification of iron overload can also made using "IDEAL-IQ" through measurement of R2* from the R2* map. R2* is the rate of signal decay in the liver and is measured in s^{-1} (or 1/s, but ***not*** Hz). R2* is linearly related to liver iron concentration (mg iron / g dry liver or mg Fe / g dw). The calibration curves to convert R2* to liver iron concentration will be available in the near future. R2* is well validated as a robust, accurate and relatively precise biomarker of iron concentration.
   a. **Measurement of R2* from ROI's:** The principles of ROI selection are the same as for PDFF.
   b. **R2*:** Similarly, I would recommend measurement of 2-4 ROI's in representative regions, including the right and left lobes. Based on these measurements an approximate average value (eg. $42s^{-1}$) or a range of values (eg. 42-$52s^{-1}$) that reflects heterogeneity can be reported. Further, the test-retest variability of R2* measurements is approximately $17s^{-1}$ (95% CI) when multiple ROI's are measured. For this reason, please report to the nearest integer, eg. $42s^{-1}$, not $42.3s^{-1}$. At 1.5T, the normal value of R2* is below approximately $60s^{-1}$. At 3.0T, the R2* essentially doubles, so the normal value of R2* is below $120s^{-1}$. For this reason, it is ***critical*** to know the field strength at which IDEAL-IQ was performed.
   c. **LIC (Liver Iron Concentration):** very recently, we have completed calibration of R2* measurements at 1.5T and 3.0T. This allows for conversion of R2* values into LIC values using the following question for 1.5T

$$\text{LIC (mg Fe / g dry liver)} = 0.026 \times R2^* \ (s^{-1}) + 0.07 \qquad [1]$$

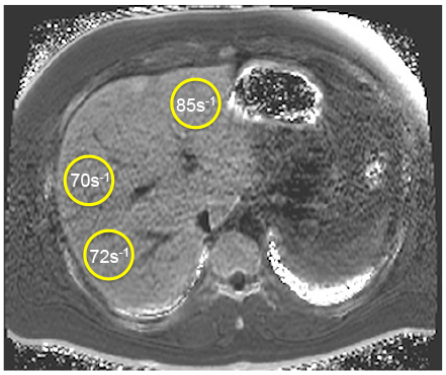
   and the following equation for 3.0T

$$\text{LIC (mg Fe / g dry liver)} = 0.014 \times R2^* \ (s^{-1}) + 0.06 \qquad [2]$$

   Further, the following table illustrates the severity of iron overload

LIC Range (mg Fe/g dw)	**R2* at 1.5T** (s^{-1})	**R2* at 3T** (s^{-1})	**Subjective Severity**
0.17-1.8	<67	<124	Normal
1.8-3.2	67 - 119	124 - 223	Mild iron overload
3.2-7.0	120 - 266	224 - 495	Moderate iron overload
7.0-15.0	267 -573	496 - 1066	Severe iron overload
>15.0	>574	>1067	Extreme iron overload

   Suggested dictation: "The study was performed at 1.5T / 3.0T. Based on measurements in multiple regions of interest, the R2* of the liver is [ ]s^{-1} (or ranges from [ ] – [ ]s^{-1}), which corresponds to a liver iron concentration (LIC) of [ ] mg Fe/g dw (or ranges from [ ] – [ ] mg Fe/g dw), which is [Subjective Severity]." Please comment if there are changes from prior studies.
   d. **Pitfalls:** There are four pitfalls of R2* measurements. First, any significant motion or ghosting artifacts can corrupt R2* measurements, and avoid measurements in blood vessels. Second, water-fat swapping occasionally occurs, particularly at the dome of the liver. R2* values in areas of swapping are not valid. For this reason, review PDFF and R2* maps together. Third, macroscopic susceptibility from air the lungs, stomach or colon can lead to artifactually high measurements of R2*. I recommend that ROI's for R2* measurements avoid the dome of the liver or areas not close to the colon or stomach. Finally, in patients with very severe iron overload (~R2*>400 s^{-1} at 1.5T and ~R2*>800 s^{-1}at 3.0T) the calculated R2* value is valid, but less precise and less accurate. This means that small apparent changes in R2* between serial exams may not represent real changes. Care should be taken when drawing conclusions about changes in iron concentration at very high R2* values.



R2* Map

Figure 2: Measurement of R2* from R2* Map. Place several ROI's in representative slices and areas being sure to sample right and left lobes. Avoid ROI's close to the lung bases, stomach or colon. Report an approximate average or a range if there is marked heterogeneity. Report to the nearest integer. In this case, I would recommend reporting as follows. "This study was performed at 1.5T. R2* is mildly elevated, ranging from approximately 70-85 1/s (normal < 60 1/s at 1.5T and < 120 1/s at 3.0T)".

3. **Liver Stiffness**: MR elastography (MRE) is available on MR4, MR5, MR6 and at AFCH only. MRE is part of the steatosis / fibrosis protocol and can also be added to any liver exam. However, it requires at least 4 breath-holds and should ***not*** be added to the limited fat/iron quantification protocol. Any protocol that uses MRE should be either a full MRI abdomen without contrast, or MRI abdomen without and with contrast. MRE measures the shear stiffness in the liver (units = kPa), and has demonstrated strong correlation with increasing stage of fibrosis. A succinct but complete overview can be found in: Taouli B, Ehman RL, Reeder SB, AJR 2009; 193:14-27.

   a. **Measurement of stiffness from ROI's:** There are only 4 slices acquired with MRE. These are positioned in a standard location, with one slice through the caudate, and two above and one below. This is intentional to ensure that serial studies have reproducible sampling of the liver. I would recommend measuring 1 ROI per slice, in 1-3 slices. To make a stiffness measurement first review the animated wave images. Choose an ROI based on a region with good wave amplitude (brightness) and where the waves are parallel to one another. Either the black and white or the colour wave images can be used for this. The waves are easier to see in colour. Based on a favourable location in the wave images, place an ROI on the ***grey scale*** stiffness map. The units from the ROI are Pascals (divide by 1000 to get kPa). There are colour stiffness maps as well, but the number in the colour stiffness map is not meaningful. Finally, one of the colour stiffness maps has a grid pattern superimposed. This is a "confidence map". Areas that have superimposed grid are regions that are not valid. I have found this grid to be overly aggressive and if the waves are parallel and visible, the measurement from the grey scale stiffness map should be valid.

   b. **Reporting:** the precision (variability) of MRE stiffness measurements is ~12% (95% CI). Therefore, I would report the value of the stiffness to the nearest decimal, eg. 2.1 kPa. If there is considerable heterogeneity between slices, report a range of values. When comparing to prior studies, please attempt to use the same region of the liver, and also comment if there are any changes from prior studies. The normal stiffness of the liver is typically ~2kPa.
      i. ***For patients with hepatitis C:*** please use the following thresholds, based on Ichikawa et al Magn Reson Sci, 11(4): 291-297, 2012:
         < 2.3kPa = No fibrosis
         2.3 to 3.1 = Stage 1 Fibrosis (F1)
         3.2 to 3.9 = Stage 2 Fibrosis (F2)
         4.0 to 4.5 = Stage 3 Fibrosis (F3)
         >4.5 = Cirrhosis (F4)
         Suggested dictation: "MR elastography demonstrated a stiffness of [X]kPa, which is [normal / abnormal (normal < 2.3kPa)], consistent with stage [X] fibrosis [FX] in patients with hepatitis C, based on Ichikawa et al Magn Reson Sci, 11(4): 291-297, 2012".

ii. ***For patients with other forms of diffuse liver disease (not hepatitis C):*** please use the following threshold values based on a series of MR-biopsy correlation studies in 450 patients performed at the Mayo Clinic:

< 2.5kPa = Normal
2.5 to 2.9 = Normal or Inflammation
3.0 to 3.5 = Stage 1 Fibrosis
3.6 to 4.0 = Stage 2 Fibrosis
4.1 to 5.0 = Stage 3 Fibrosis
>5.0 = Cirrhosis

Suggested dictation: "MR elastography demonstrated a stiffness of [X]kPa, which is normal / abnormal (normal < 2.5kPa), indicating the presence of inflammation and/or fibrosis (if abnormal)". I do not think it's necessary to comment on the presence of inflammation or fibrosis stage, but this is available in case the clinicians are interested.

c. **Pitfalls:** There are two main pitfalls of MRE. In the presence of iron overload, there may be insufficient signal and the waves may appear highly disorganized. If the wave images do not make sense, look at the IOP, R2* maps or T2 weighted images to look for iron overload. In addition, patients with ***normal*** livers have less penetration and sometimes have a very small area (or none!) that is not cross hatched on the confidence map. If the waves are present, and very close together, you can make the qualitative assessment that the stiffness is normal. Fortunately, as the liver gets stiffer, waves penetrate the liver more easily and the measurement is more reliable.

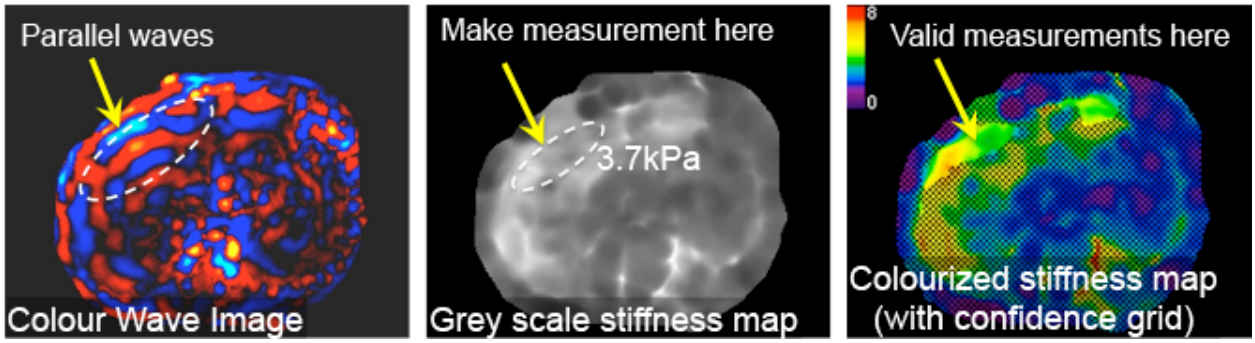


Figure 3: MRE wave images (left) are used to identify high amplitude, parallel waves. Using that region, choose an ROI in the grey scale stiffness map. The colour map with confidence grid can also be used to help select a ROI. Report the stiffness to the nearest 1/10th of a kPa. In this case I would dictate "MR elastography demonstrated an elevated stiffness of 3.7kPa (normal < 2.5kPa), indicating the presence of inflammation and/or fibrosis."