# Iron Quantification with LiverLab

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Multi-echo Dixon VIBE contained in LiverLab provides liver fat fraction values which are corrected for the effects of transversal relaxation. By doing this, it also provides a simultaneous estimation of that transversal relaxation time T2*, which is corrected for fat signal effects, herefafter called $T2_c$*. The reciprocal value of this estimate, fat-corrected $R2_c$* = 1/ $T2_c$*, can be used, within limits, to assess liver iron concentration (LIC). This note provides some guidelines for doing that.

## MR liver iron quantification

Liver iron content is an important clinical biomarker. It can be assessed by various methods, including biopsy, which is still considered to be the gold standard but potentially harmful for the patient and suffering from a large sampling variability. It is also possible to use biomagnetic susceptibility measured with SQUID devices, but these are few and far between.

Alternatively, the effect of iron on the MR signal can be exploited. One such technique uses the transverse relaxation rate R2 = 1/T2 from spin-echo images, calibrated against biopsy [1], and this has been cast into a commercial product with regulatory approval: FerriScan (Resonance Health, Claremont, WA, Australia). Another, larger group of published techniques uses the transverse relaxation rate R2* = 1/T2* from 2D gradient-echo images, also calibrated against biopsy [2-5]. Unfortunately, these calibrations vary, if not by very much. Potential reasons for these variations are differences in the reference histology procedure [6], but also in data acquisition, and probably most importantly, in the R2* evaluation procedures, and there mainly in how they deal with noise. Some techniques use a constant noise offset as model parameter, others subtract a measured noise level, or truncate the number of echoes used. Fortunately, it seems that different techniques, despite different calibrations, lead to comparable LIC values [7]. However, the previously published methods do not take fat signal effects into account.

In order for the $R2_c$* to be truly quantitative, the data fitting procedure needs to correct for confounding effects, in particular image noise and signal modulations from fat [8]. A disadvantage of taking the fat signal into account is that any erroneous swaps of fat and water not only lead to errors in the estimation of the fat fraction (in that case, it is *not* equal to one minus the water fraction), but also to a confounded estimation of $R2_c$*. An important additional effect to consider is that liver R2* scales almost linearly with field strength [9, 10].

## R2* from multi-echo Dixon VIBE

The multi-step adaptive fitting approach in [11] was originally designed for fat quantification, and its signal model contains terms for water and fat, as well as R2*; the inner fitting step uses magnitude data; appropriate protocols have to be used so that the later echo images still have sufficient signal-to-noise ratio (SNR).

### Protocol design

In general, measurement protocols for R2* estimation need echo times which are as short as possible to capture rapid signal decay [5]. On the other hand, the initial water/fat separation step in multi-echo Dixon VIBE works best when the first two echo times are at or near opposed- and in-phase. At 3T, these two requirements are not in conflict (the first opposed-phase echo time is 1.23 ms), but at 1.5T, echo times near opposed- and in-phase are preferred. To reduce noise bias, the SNR of the acquisition should be as high as possible, so smaller image matrices and moderate parallel imaging (iPAT) acceleration factors are helpful. Asymmetric data acquisition should be avoided [12]. Finally, since the later echoes will always be dominated by noise if R2* is very high, it may be advantageous to use only 4 instead of the standard number of 6 echoes. Recommended protocols are listed in Table 1.

| | 1.5T | 3T |
|---|---|---|
| **TE [ms]** | 1.1, 2.2, 3.3, 4.4 (5.5, 9.5)[1] | min, typ. 1.1, 2.2, 3.3, ... |
| **Matrix** | 160 | |
| **Bandwidth [Hz/pixel]** | typ. 1100 for minimum first TE | |
| **Flip angle [°]** | 6[2] | 5[2] |
| **TR [ms]** | min, typ. 11 | |
| **Asymmetric echo** | off | |
| **Partial Fourier** | off | |
| **Parallel imaging** | CAIPIRINHA x3 (abdomen preset: PE x1, 3D x3, reordering shift 2) | |

**Table 1:** Recommended protocol values for iron estimation with multi-echo Dixon VIBE.

[1] At very high R2*, leaving out the later echoes will help to avoid noise bias.
[2] Depending on TR. Higher flip angles will improve SNR, but introduce a T1 bias in the fat fraction values.

### Data interpretation

A mean $R2_c^*$ can be measured from the corresponding parameter maps via a region-of-interest (ROI) using any viewing software. In multi-echo Dixon VIBE, one grey scale unit corresponds to 1 $s^{-1}$, as it is also noted in the DICOM image comment. This value can then be multiplied with the iron calibration conversion factor of choice (see below). Several ROIs in different slices can be used to assess spatial heterogeneity of liver iron overload, or to average results. As long as the inline liver segmentation contained in LiverLab was successful, the average R2* across the entire liver can also be used, but it has to be noted that structures inside the liver which are not liver parenchyma, e.g. large vessels, are not automatically excluded.

### Iron calibration

So far, no direct iron calibration for fat-corrected $R2_c^*$ against biopsy has been published. However, initial comparisons between $R2_c^*$ and LIC from FerriScan come to similar conclusions [13, 14]. Figure 1 lists a number of iron calibration curves.

Noise bias on magnitude images will in general lead to under-estimation of R2*, and requires an increased calibration factor. Depending on the noise level, this effect sets in when T2* approaches twice the first TE, which is typically ~1 ms. Consequently, R2* values above 500 $s^{-1}$ should always be assumed to be under-estimated; this means that currently severe iron overload cannot be reliably detected at 3T using LiverLab. It can, however, be assumed that R2* estimates are reproducible up to ~1000 $s^{-1}$ as long as the protocol is held constant, the setup of patient and receive coils is comparable, and that there are no fat/water swaps, which would make follow-up examinations possible.

Trying to summarize the current state of knowledge, and taking into account the tendencies of the individual original techniques to under- or over-estimate R2*, a tentative working value for converting $R2_c^*$ from multi-echo Dixon VIBE in units of $s^{-1}$ into LIC in units of mg/g dry weight (dw) at 1.5T seems to be approximately 0.032 mg/g $Fe_{dw}/s^{-1}$, e.g.

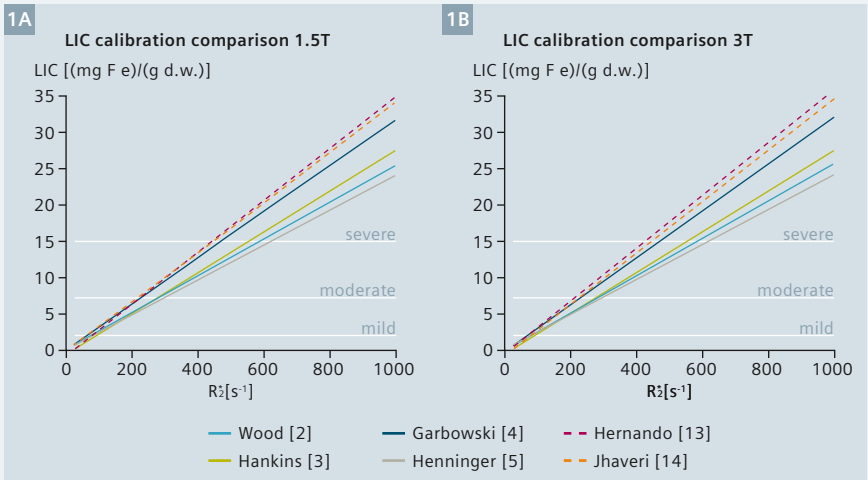
**Examplary calculation for 1.5T**

$R2_c^* = 200\ s^{-1}$

$\rightarrow LIC = 0.032 \cdot 200\ mg/g\ Fe_{dw}$
$= 6.4\ mg/g\ Fe_{dw}$

Most iron calibrations contain, beside the proportionality factor, an offset in mg/g $Fe_{dw}$, which is positive for some calibrations, and negative for others. In the absence of further evidence, we suggest to assume this offset to be zero, which seems to be supported by simulations [15]. Using the field-strength dependence as reported in [9], and typical Larmor frequency values of Siemens MR scanners, this translates into a conversion factor at 3T of approximately 0.017 mg/g $Fe_{dw}/s^{-1}$. Table 2 summarizes values which take into account an assumed under-estimation towards high R2* values.

However, for now, the LIC values calculated using LiverLab always have to be interpreted with care by an experienced user.




**1** Existing iron calibrations. **(1A)** 1.5T; solid lines are calibrated against biopsy results, dashed lines are calibrated against FerriScan. **(1B)** 3T; there are no biopsy-based calibrations; results projected from 1.5T using [9], except Hernando [8].

| | 1.5T | 3T[3] |
|---|---|---|
| **mild (LIC ≥ 2 mg/g $Fe_{dw}$)** | 65 $s^{-1}$ | 115 $s^{-1}$ |
| **moderate (LIC ≥ 7 mg/g $Fe_{dw}$)** | 215 $s^{-1}$ | 400 $s^{-1}$ |
| **severe (LIC ≥ 15 mg/g $Fe_{dw}$)** | 440 $s^{-1}$ | n/a |

Values in this table are a tentative and preliminary projection from existing studies, taking into account some expected under-estimation of R2* given the current limits of implementation in LiverLab.

Results will vary depending on protocol settings and image SNR, as well as on future changes in the algorithm.

**Data interpretation and diagnostic conclusions are solely in the responsibility of the user.**

**Table 2:** Tentative cut-off values of $R2_c^*$ from multi-echo Dixon VIBE for different grades of liver iron overload.

[3] 3T values are projected from 1.5T values using [9].

### Offline processing of individual echoes

Multi-echo Dixon VIBE allows exporting the individual echoes in addition to the parameter maps. In challenging cases, or when an external cross-calibration is desired, these can be processed manually with custom software, see for example [16].

Likewise, the data acquisition protocols of existing iron calibrations, e.g. [3], or the signal-intensity ratio method described in [17], can easily be reproduced using the product 2D GRE sequence, and the results compared to those of LiverLab as long as the appropriate post-processing is used.

## Conclusion and outlook

Although multi-echo Dixon VIBE from LiverLab was originally designed for liver fat evaluation, the $R2_c$* values, used with care, allow estimating liver iron concentration within limits.

There are predevelopment activities and ongoing studies to extend multi-echo Dixon VIBE to properly calibrated iron quantification in a future software version. We encourage all users of LiverLab to share their experience using the current product version.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## Further Reading

An Efficient Workflow for Quantifying Hepatic Lipid and Iron Deposition using LiverLab

*Puneet Sharma, Diego Martin (University of Arizona, Tucson, AZ, USA)*, MAGNETOM Flash #58 (3/2014)

Case Study LiverLab

*Stephan Kannengiesser et al. (Siemens Healthcare, Erlangen, Germany)*, MAGNETOM Flash #58 (3/2014)

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