Routine quantification of liver iron by MRI

Y. Gandon, A. Paisant, G. d'Assignies, C. Chargeboeuf, E. Bannier, H. Saint-Jalmes.

*Prof. Yves Gandon is the creator of the **MRQuantif** java software freely avalaible on www.mrquantif.org*

Medical Imaging
University Hospitals of Rennes – FR

INSERM – LTSI - UMR 1099

Clinical background

Physics background

In practice

Pittfalls

What are the main causes?

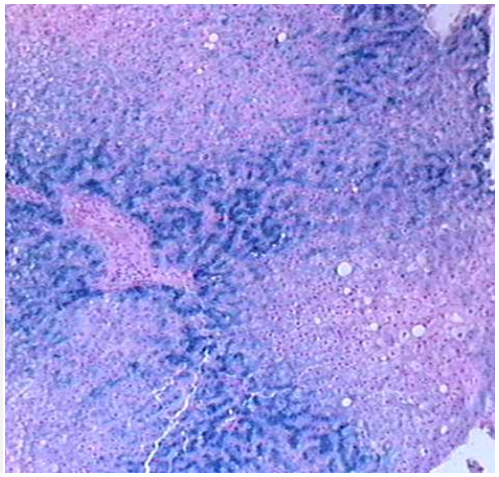
- Genetic hemochromatosis:
  - constant but variable hepatic iron overload, within hepatocytes,
  - no splenic iron overload except in a rare type of mutation (type 4),
  - main risk is cirrhosis with hepatocellular carcinoma.
- Hemolytic anemias or repeated transfusions:
  - iron overload of the reticulo-endothelial system, including spleen,
  - main risk is cardiac failure.
- Dysmetabolic iron overload syndrom:
  - slight iron overload of the liver and spleen,
  - with associated steatosis,
  - main risk is evolution to NASH and cirrhosis.

MRI quantification indications?

- Not really required in genetic hemochromatosis:
  - diagnosis is done by genetic test
  - ferritinemia could be sufficient to follow effect of repeated phlebotomies
  - It just helps to predict the treatment length
- Could be useful in hematologic disorders:
  - to follow treatment by chelation
  - to quantify simultaneously cardiac iron
- Helpful in DIOS or unexplained hyperferritinemia:
  - to determine if there is an hepatic and splenic iron overload
  - and also to better quantify liver steatosis

What is the gold standard?

- Iron is detected by **Perls** staining showing dark blue spots which corresponds to iron deposition.



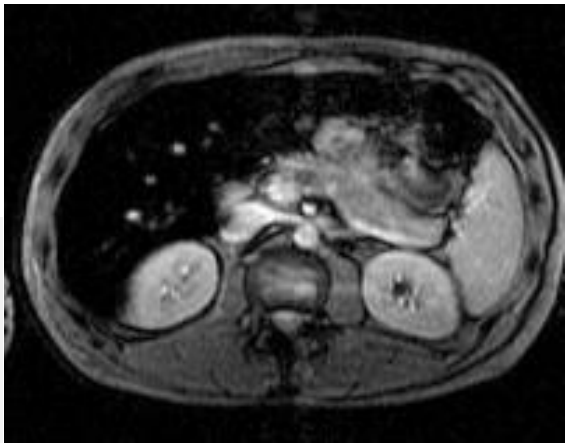
Iron deposits located around a portal space. This is characteristic of a genetic hemochromatosis.

- But liver (hepatic) iron concentration (**LIC or HIC**) is determined by biochemical analysis of the biopsy core and is expressed :
  - in mg/g with a upper normal limit of **2 mg/g**
  - or in µmol/g with a upper normal limit of **36 µmol/g**

1 mg/g = 18 µmol/g

Effect of iron on MRI signal?

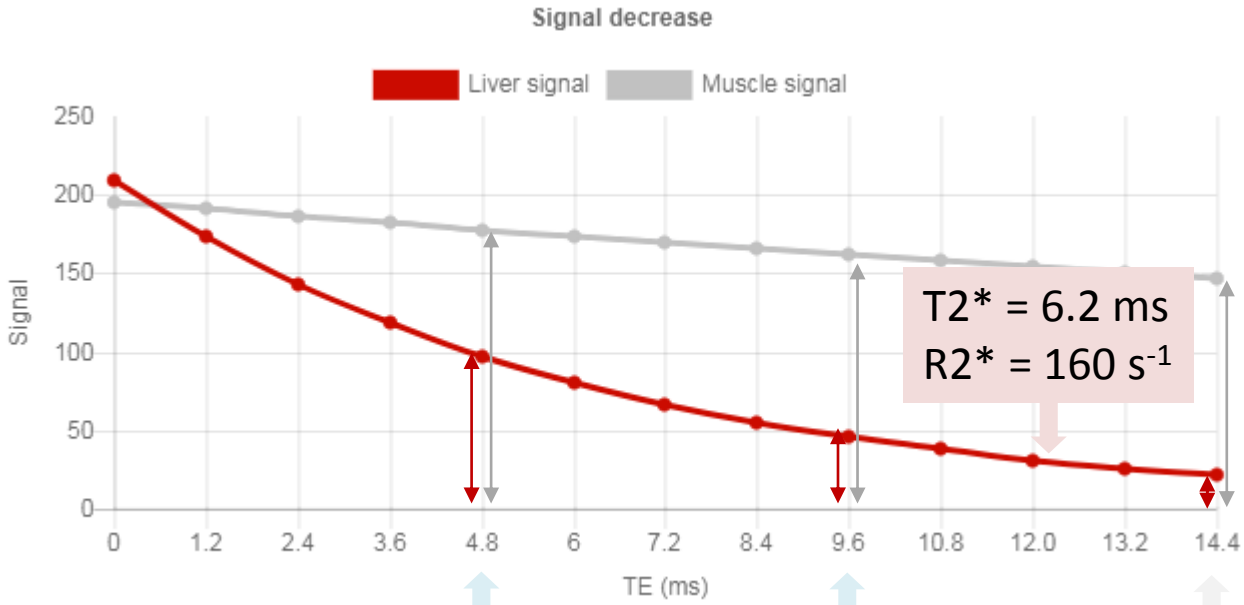
- Iron is stored as ferritin in 12 nm boxes containing 4500 Fe^{3+} each.
- This produces a **superparamagnetic** effect with a predominant T2* decrease, leading to an **hyposignal** intensity which is stronger:
  - with GRE sequences, more sensitives to iron overload
  - when TE increases
  - if magnetic field is stronger



Major decrease of the liver signal intensity in comparison to that of the paraspinous muscles. No decrease of the splenic signal in this genetic hemochromatosis.

What are the two MRI methods?

- **Relaxometry** by calculating T2[1] (or R2) from a multiecho (ME) SE sequence or more frequently T2* (or R2*) from a ME GRE sequence
- Liver to muscle **Signal Intensity Ratios (SIR)** using several (in-phase) TEs of dedicated GRE sequences. To compare the signal this sequence must use the **BODY COIL.** The ratio selected is preferably between 0.25 and 0.7.

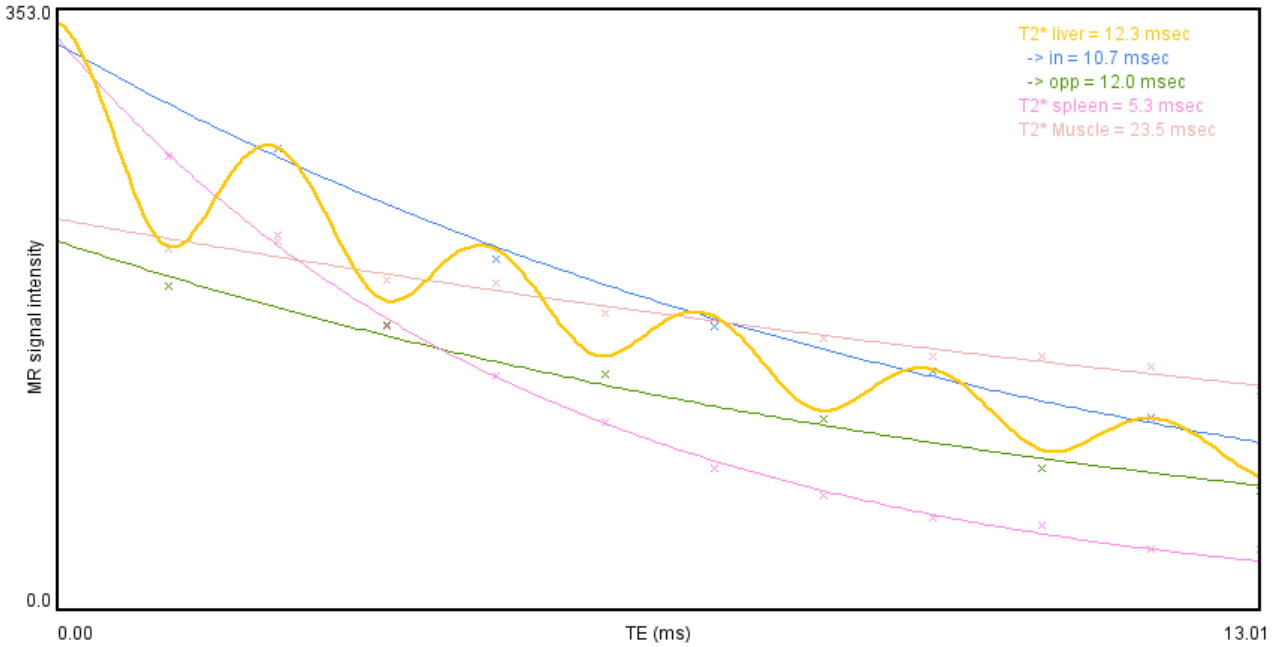


[1] Only proposed by an autralian team as a commercial FDA approved test named FerriScan®.

How T2* is calculated?

- Liver signal intensities should be measured at the same location for each TE of a ME GRE sequence.
- A curve is fitted with these values using this equation : $signal = signal0 - exp^{(-TE/T2^*)} + offset$
- Offset (corresponding to background noise) can be subtracted or used as a threshold limit for truncation.
- A more complex equation can be used to integrate the phase variation due to the fat.

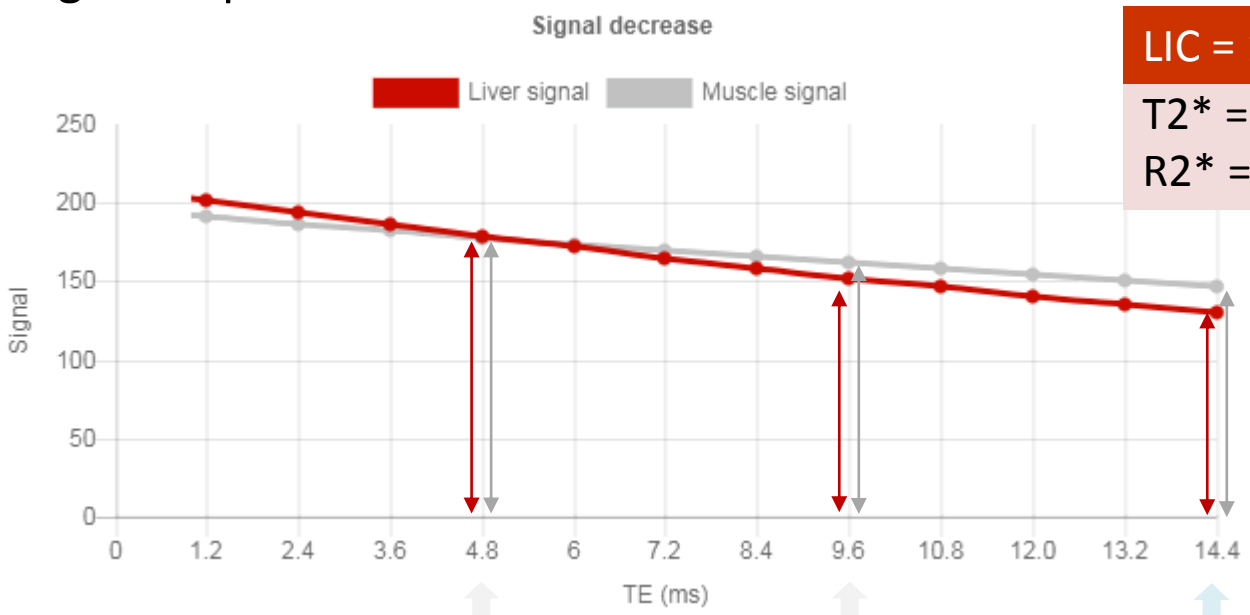
Another example with significant steatosis responsible of a cyclic ondulation of the liver signal. In that case, MRQuantif curve fitting is taking in account the phase signal variation.



What happens in case of normal liver?

1.5 Tesla

- **LIC < 36 µmol/g**:
  - T2* > 18 ms and R2* < 55 s^{-1}
  - Liver signal intensity is close to that of muscle, SIR is > 0.8 including on long TE sequence



LIC = 10µml
T2* = 30 ms
R2* = 33 s^{-1}

1st in-phase TE
L/M = 1.0

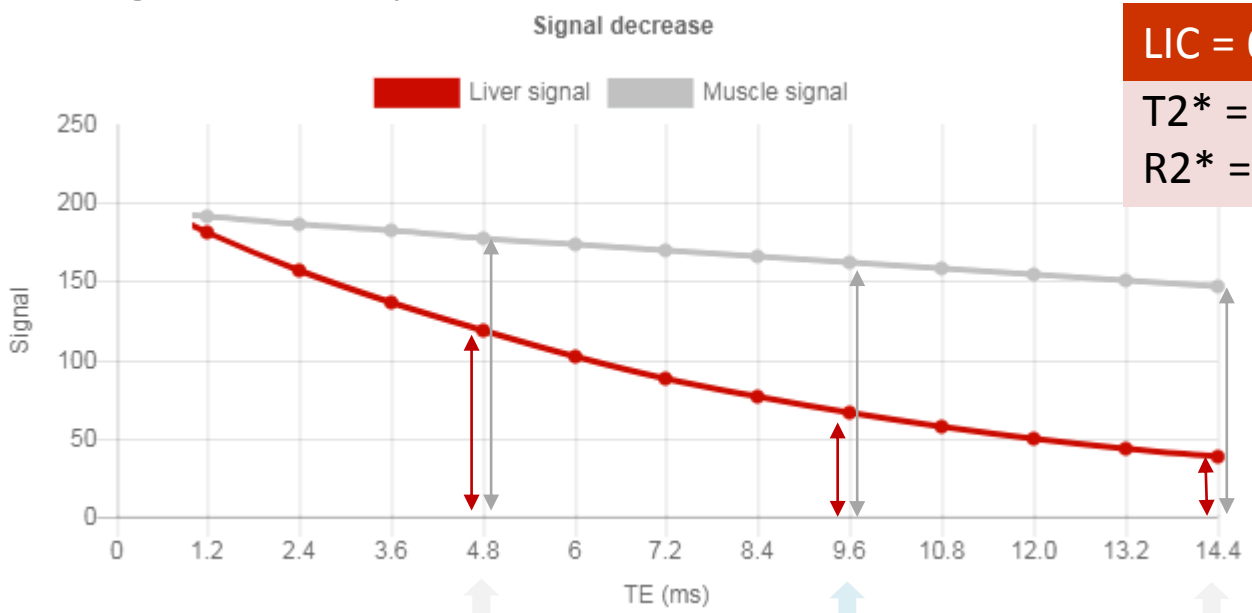
2nd in-phase TE
L/M = 0.94

3rd in-phase TE
L/M = 0.88

In case of slight iron overload?

1.5 Tesla

- **LIC = 36-72 µmol/g**:
  - T2* = 18ms down to 7 ms and R2* = 55 s^{-1} up to 145 s^{-1}
  - Liver signal intensity decreases below that of the muscle, particularly on long TE GRE sequence



LIC = 60µml
T2* = 8.3 ms
R2* = 120 s^{-1}

1st in-phase TE
L/M = 0.66

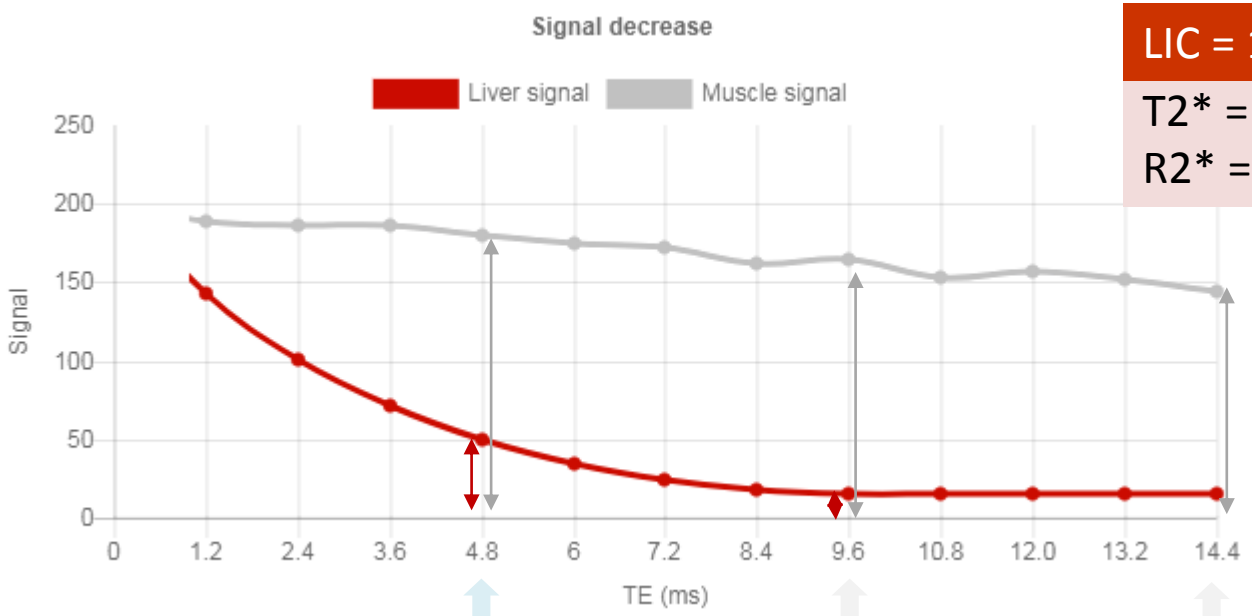
2nd in-phase TE
L/M = 0.41

3rd in-phase TE
L/M = 0.25

In case of moderate iron overload?

1.5 Tesla

- **LIC = 72-200 µmol/g**:
  - T2* = 7ms down to 2.5 ms and R2* = 145 s^{-1} up to 400 s^{-1}
  - Liver signal stays superior to the noise only on 1st in-phase TE with SIR between 0.5 and 0.2



LIC = 150 µml
T2* = 3.3 ms
R2* = 300 s^{-1}

1st in-phase TE
L/M = 0.27

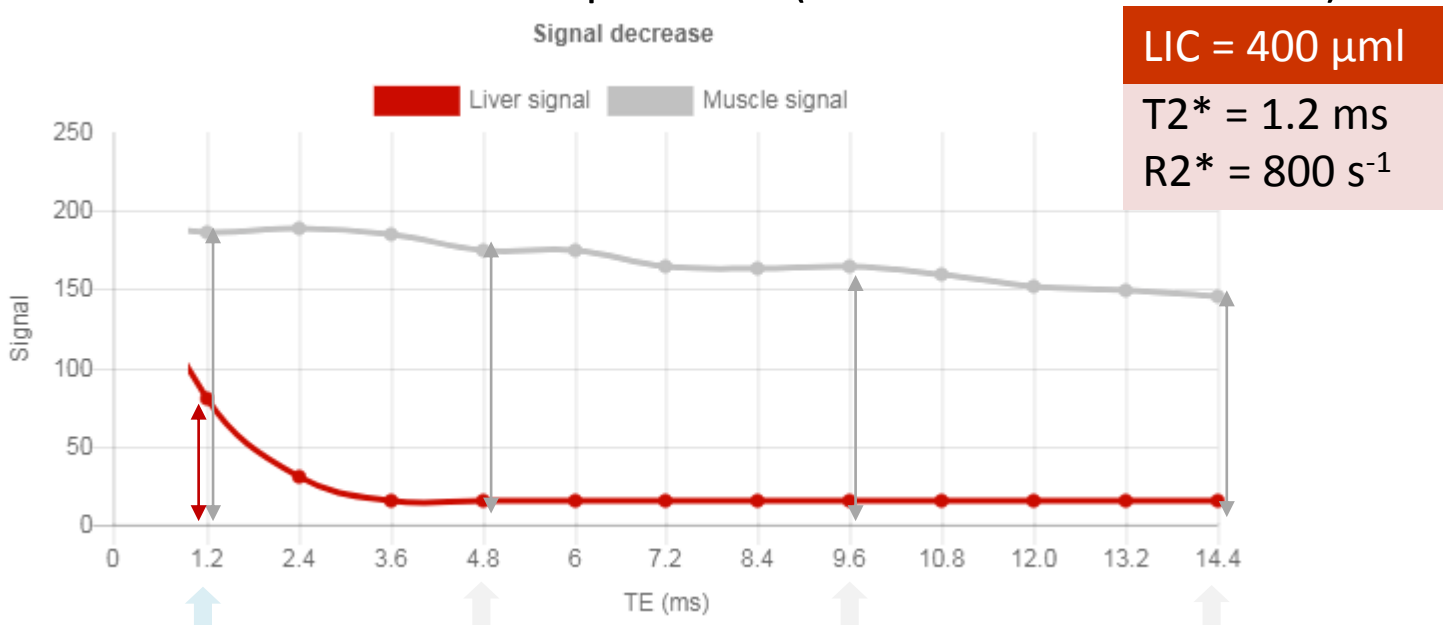
2nd in-phase TE
L/M < 0.1

3rd in-phase TE
L/M < 0.1

In case of high iron overload?

1.5 Tesla

- **LIC > 200 µmol/g**:
  - T2* < 2.5 ms and R2* > 300 s^{-1} , method is not accurate if first TE is not short enough, ie > 1 ms
  - SIR could use a shorter out-phase TE (after steatosis exclusion)



LIC = 400 µml
T2* = 1.2 ms
R2* = 800 s^{-1}

Out-phase TE
L/M = 0.41

1st in-phase TE
L/M < 0.1

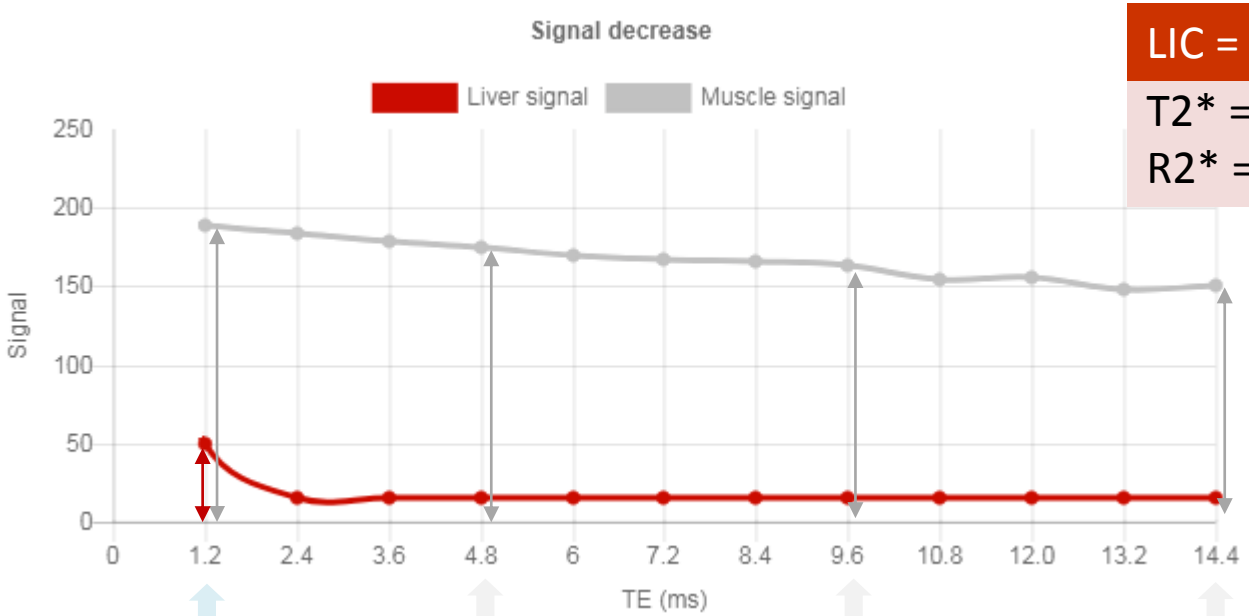
2nd in-phase TE
L/M < 0.1

3rd in-phase TE
L/M < 0.1

In case of major iron overload?

1.5 Tesla

- **LIC > 500 µmol/g**:
  - The T2* can be strongly overestimated if the first TE is not below 1 ms
  - SIR should be used to avoid iron assessment errors



LIC = 600 µml
T2* = 0.8 ms
R2* = 1200 s^{-1}

Out-phase TE
L/M = 0.26

1st in-phase TE
L/M < 0.1

2nd in-phase TE
L/M < 0.1

3rd in-phase TE
L/M < 0.1

What happens at 3T?

- Effect of iron is **two times stronger**:
  - the T2* is divided by 2,
  - and the R2* is multiplied by 2.
- The TE should be divided by 2 to get a similar signal.
- Then the **accurate determination of this shorter T2* can become difficult**.
- When using a first TE about 1 ms, the limitation occurs even for moderate overloads.
- A shorter first TE, for example of 0.5 ms, is difficult to obtain in routine.
- So the **SIR method is frequently needed as a complement**.

So which method to use?

- If you can get a ME GRE sequence with your MRI device, **T2*/R2* calculation** should be preferred,
- **except** in case of high overload at 1.5T, or even moderate overload at 3T, when liver signal intensity decreases strongly on the first echo: it is necessary to have at least 2 echoes keeping a signal to calculate correctly T2*.
- If there is a strong decrease in the signal, the **SIR method** must be performed to avoid major errors.

R2* to LIC?

- Here are the 5 main articles analyzing the correlation between the R2* and the LIC:

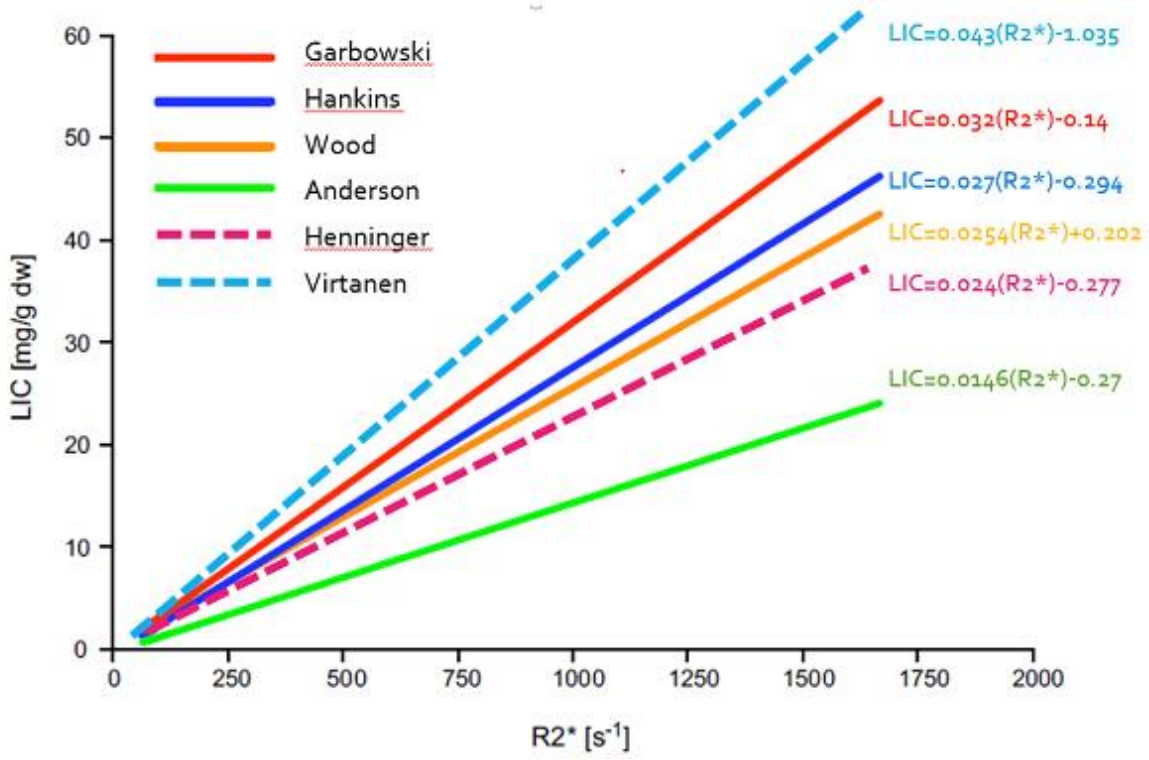
Ref	Patients	With biopsies	LIC range (mg/g)	Sequence	Matrix	TR (ms)	FA (°)	TE-min (ms)	delta-TE (ms)	N TEs	TE-max (ms)	Comment	Method	Correlation (R)
Anderson Eur Heart J 2001	27 patients	**27 (29 biopsies):** β-thalassemia	1-26	GRE mono echo	96×128	200	20	**2.2**	2.56	8	20.1		offset	0.68 (fibrosis) 0.93 (others)
Wood Blood 2005	102 patients + 13 controls	**22**: thalassemia major (n=9), sickle cell disease (n=10), thalassemia intermedia (n=2), Blackfan-Diamond syndrome (n=1)	1.3-32.9 et 57.8	GRE mono echo	64x64	25	20	**0.8**	0.25	16	4.8	Controls: R2* = 39 s^{-1} T2* = 25 ms.	offset	0.97
Hankins Blood 2009	43 patients	**43**: sickle cell disease (n=32), thalassemia major (n=6), bone marrow failure (n=5)	0.6-27.6 NB: 2 <2mg/g	GRE multi echoes	?	?	?	**1.1**	0.8	20	17,3		truncated	0.97
Garbowski J Cardiovasc Magn Reson 2014	121 patients 31 controls	**25 (50 biopsies)**: βthalassemia (n=20), Blackfan-Diamond syndrome (n=1), congenital sideroblastic anemia (n=2), pyruvate kinase deficiency (n=1)	1.7-42.3 NB: 1 <2mg/g	GRE multi echoes	?	?	?	**1.1**	0.8	20	17,3	Controls: R2* = 37 s^{-1} T2* = 27 ms.	truncated	0.94
Henninger RöFo 2015	17 patients	**17**: hemochromatosis (n=10), DIOS (n=2), aceruloplasminemia (n=2), congenital sideroblastic anemia (n=1), spur cell aenemia (n=1)	0.92-11.65 NB: 4 <2mg/g	GRE multi echoes	128x128	200	20	**0.99**	1.41	12	16.5	fat suppression	truncated	0.92
	Total of 161 biopsies													

- And our experience at 3T:

Ref	Patients	With biopsies	LIC range (mg/g)	Sequence	Matrix	TR (ms)	FA (°)	TE-min (ms)	delta-TE (ms)	N TEs	TE-max (ms)	Comment	Method	Correlation (R)
d'Assignies 2017	105 patients	**105:** hemochromatosis (n=31) DIOS (n=22) others (n=3) controls (n=49)	0-35	GRE multi echo	106×128	120	20	**1.2**	1.2	10	12		subtraction	0.95
	A total of 105 biopsies													

Correlation between R2* and LIC?

- There are differences between the parameters of the formula converting R2* to LIC **(expressed here in mg/g)**



- To be converted **in µmol/g** , R2* should be divided by a value between 1.8 (Garbowski) and 2.5 (Henninger).

SIR to LIC?

- Here are the 4 main articles analyzing the correlation between the SIR and the LIC:

Ref	Patients	With biopsies	LIC range (µmolg/g)	Sequence	Matrix	TR (ms)	FA (°)	TE-min (ms)	N TEs	TE-max (ms)	Method	Correlation (R)
Gandon The Lancet 2004	113 patients + 61 controls	**174**: with cirhosis (n=39), with steatosis (n=31)	0-709	GRE mono echo	256×128	120	20	**4**	4	21	on-line calculator	0.87-0.92
Alustiza Radiology 2004	44 patients + 68 controls	**112**	0-390	GRE mono echo	256×128	120	20	**4**	3	21	formula	0.94
Rose Eur J Haematol 2006	25 patients + 2 controls	**27**	25-972	GRE mono echo	256×128	120	20	**1.8**	5	21	formula for high overload using 1.8 ms TE	0.85
Castiella Eur Radiol 2011	64 patients (20 new) + 107 controls (39 new)	112 published(Alustiza) **+59 new**	0-390	GRE mono echo	256×128	120	20	**4**	3	21	31 patients at 1T, TE 9 ms missing	0.86
	Total of 372 biopsies											

At 1.5T Alustiza SIR method is probably closer to R2* results

- And our experience at 3T:

Ref	Patients	With biopsies	LIC range (µmolg/g)	Sequence	Matrix	TR (ms)	FA (°)	TE-min (ms)	N TEs	TE-max (ms)	Method	Correlation (R)
Paisant Abd Radiol 2017	105 patients	**105:** hemochromatosis (n=31) DIOS (n=22) others (n=3) controls (n=49)	0-630	GRE mono echo	106×128	120	20	**1.2**	5	14	on-line calculator	0.96
	Total of 105 biopsies											

More detailed information on: https://imagemed.univ-rennes1.fr/en/mrquantif/quantif.php

In practice?

Can I perform a ME GRE sequence on my MRI device?

	GEMS	Philips	Siemens	…
2D ME GRE	Starmap[1] option	Standard package		
3D ME GRE (options)	IDEAL-IQ	mDixon-Quant	Liverlab with 3D VIBE-Dixon	…

With 2D ME GRE you need to have another software (such as MRQuantif[2]) or plugin to calculate T2*or R2*.

3D ME GRE sequences produce T2* or R2* maps (and Fat fraction maps)

[1] *Could be replaced by several monoecho GRE without changing calibration between them*

[2] *Free download at* https://imagemed.univ-rennes1.fr/en/mrquantif/download.php

What is needed for the SIR method?

The minimum is to use GRE sequences with these parameters:

BODY COIL

TR = 120 ms
FA = 20°

Field \ TE	opp1	in1	in2	in3	in4
1.5T	2.4 ms	**4.8 ms**	9.6 ms	**14.4 ms**	
3T	1.2 ms	2.4 ms	4.8 ms		9.6 ms

Available on all MR systems.
No option or extra software is required.

But now, use preferably a ME GRE sequence (alternating TE out/in-phase) that allows the simultaneous quantification of fat and iron with both methods, T2* and SIR.

What parameters for this ME GRE?

We propose parameters which allow to use simultaneously T2* and SIR methods.

To use SIR method, body coil must be the only one selected.

Main MRI parameters

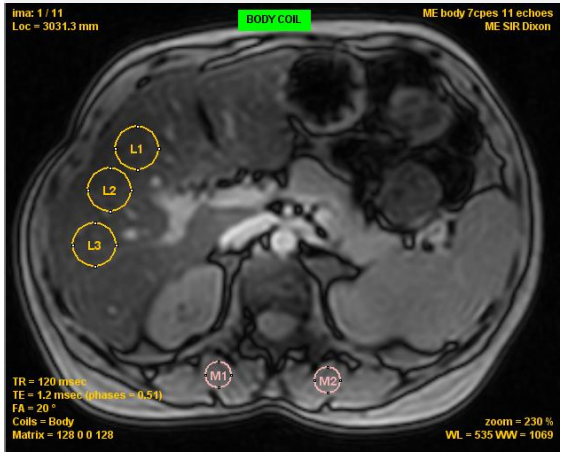
Coil	**Body (autoselection off)**
Sequence	GRE
Options	No fat saturation
TR (msec)	120 (to reduce T1 contrast)
TE (msec)	**multiple of 1.2**
FA (°)	20 (to reduce T1 contrast)
Bandwith	Adapt it to get the correct TEs
N excitations	1
Plane	Axial
N slices	Max allowed (could depend on the number of TEs ...)
Thickness	7 or 8 mm
Gap	Could be large (10mm) if you have a small number of slice
Matrix	Asymetric to reduce acquisition time, ex: 128x116
Phase	Anterior-Posterior
FOV (cm)	40
Aq. time (sec)	about 15

Protocols for various MR devices are avalaible at https://imagemed.univ-rennes1.fr/en/mrquantif/protocols.php

How to get LIC from SIR data?

- ROIs are placed on the liver and paraspinous muscles on **GRE** images obtained with the **BODY COIL**. Signal intensities values can be used with the Alustiza formula LIC (µmol/g) = e $^{(5.8-(0.9 \times LMin3) - 1.5 \times LMin1))}$ or entered in the Rennes web page.
- However, to avoid errors it is now recommended to do this with the **MRQuantif** software which controls the coil used (by reading the DICOM header).

MRQuantif software



Rennes university web page example

The first sequence has now a shorter TE to be able to quantify high overload. It is useful only if the second sequence, existing in the old protocol, shows a complete liver signal decrease. The last sequence is not mandatory, but if you use it please switch to a 19ms TE instead 21ms to better be in-phase.

Patient: Test

TR / TE / PA°	*Liver(1)*	*Liver (2)*	*Liver (3)*	*Muscle (1)*	*Muscle (2)*	*L/M*	*LIC*	*Comments*
Out (1): GRE 120 / 2 / 20°	0	0	0	0	0	0		
In (1): GRE 120 / 4 / 20°	232	228	235	189	195	1.21	81	✖ high signal, low sensitivity
In (2): GRE 120 / 9 / 20°	188	181	184	172	181	1.04	76	✖ high signal, low sensitivity
In (3): GRE 120 / 14 / 20°	95	88	91	125	128	0.72	77	✔ usable value
In (4): GRE 120 / 19 / 20°	0	0	0	0	0	0		

Results :

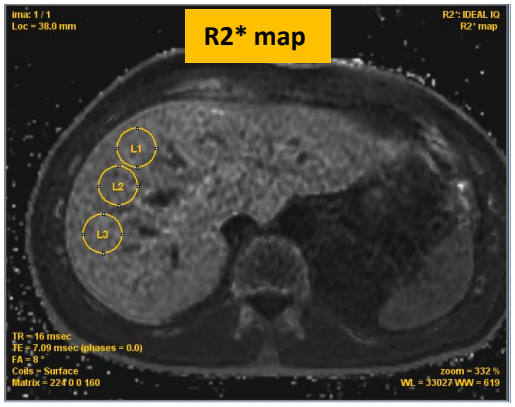
LIC estimated using TE of 14 ms: 77 (±30) µmol/g (N < 36 µmol/g)

Version: January 21th, 2018

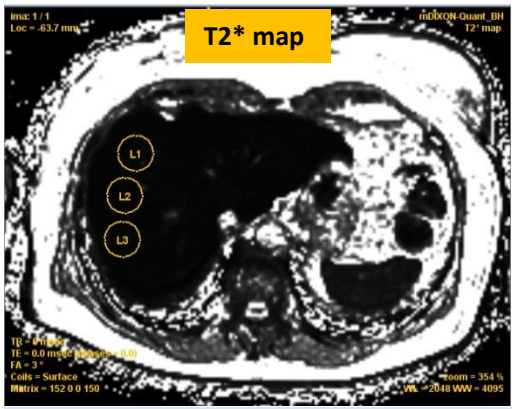
Direct link: https://imagemed.univ-rennes1.fr/en/mrquantif/online_quantif.php

How to get R2* and LIC from data?

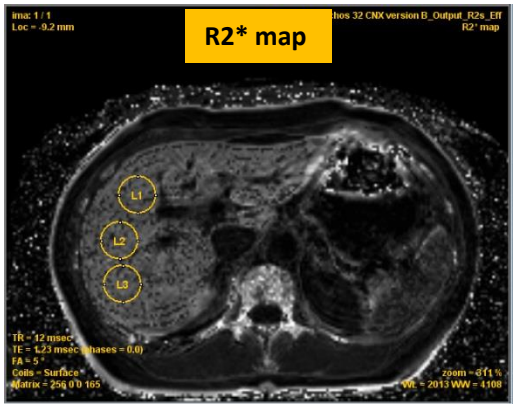
- R2* or T2* maps are built if you have acquired a 3D ME GRE sequence. The pixel value is not always standardized and may require the use of a manufacturer's software.



IDEAL IQ (GEMS)



mDIXON-Quant (Philips)



Vibe-DIXON (Siemens)

- If you got the T2* in ms calculate the R2* in s^{-1} (R2*=1000/T2*).
- At **1.5T**, I propose a conversion half-way between Wood and Garbowski formula:

LIC in µmol/g = R2*/2

- If you work with hematologists: **LIC in mg/g = LIC in µmol/g / 18**
- At **3T**, use preferably the MRQuantif software to avoid major errors due to T2* miscalculation

How to get R2* and LIC from data?

- If you don't have 3D GRE commercial option, you can use, with the same performance (or even better, cf ESGAR 2018 scientific session), the ME GRE data (preferably acquired with body coil to make a cross-check by SIR method)
- Download freely the MRQuantif software (or equivalent if you find one) and calculate the LIC from your data

And a preliminary report is produced in the selected language.

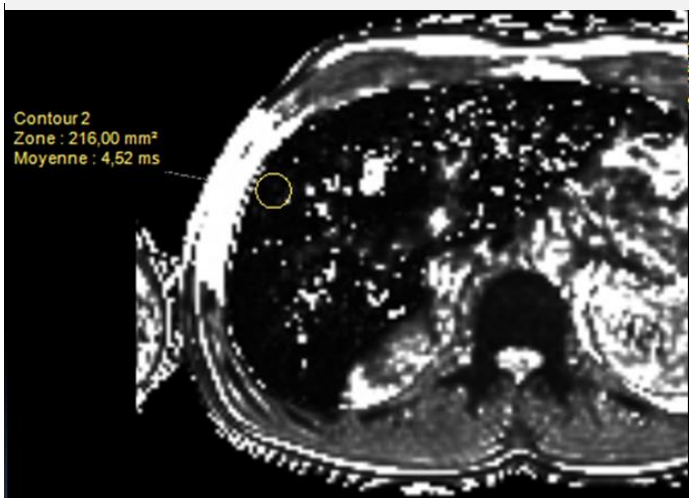
Main pittfalls

- T2* map **miscalculation**
- T2* **overestimation**
- Using the **SIR method when a surface coil** has been selected
- **Follow-up** not using the same method or the same settings.

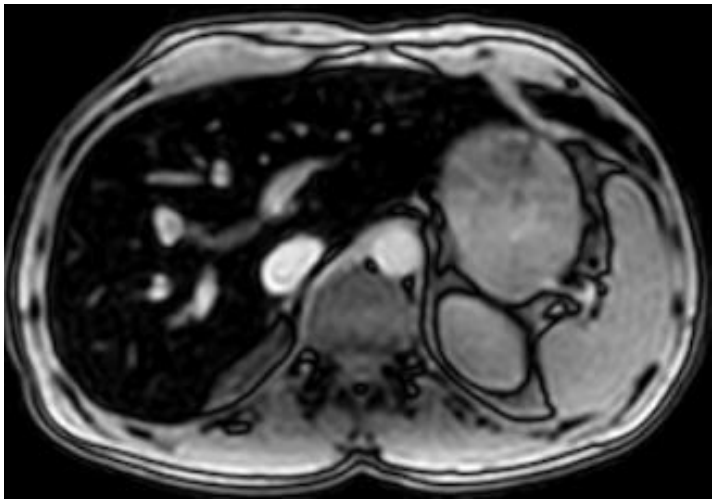
T2* map miscalculation

- T2* map pixelwise calculation is using complex formula taking in account the phase variation of signal.
- In case of strong decrease of signal, particularly at 3T, pixel to pixel variation due to the inherent noise may introduce a major **calculation error**. This occurs whith all MRI brands.

T2* = 4.52 ms - R2* = 221 ms – MR-LIC = 110 µmol/g



LIC estimated at 110 µmol/g instead of 500 µmol/g and FF = 43% instead of 0%



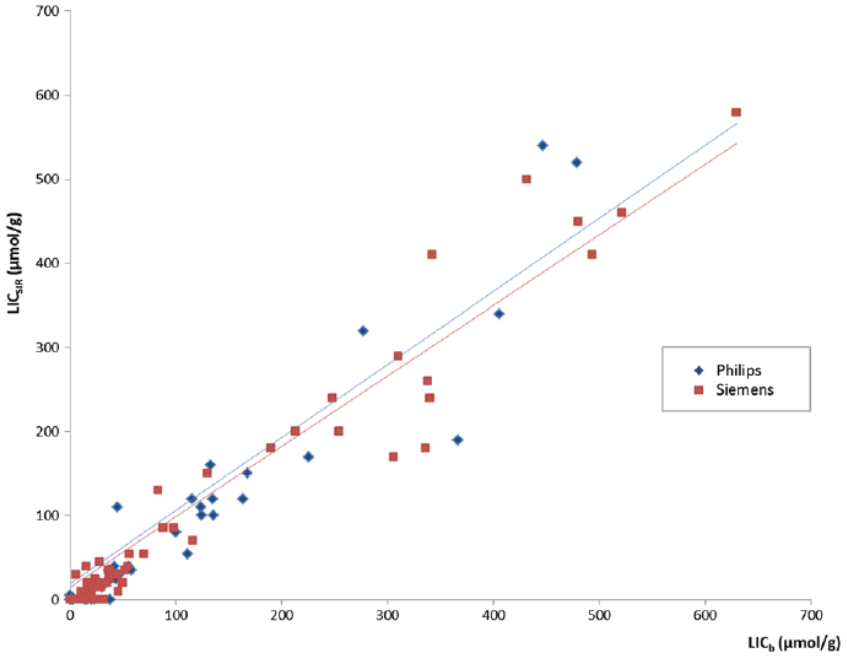
So, don't trust maps if signal is too low on first echoes

T2* limitations in case of high LIC

- In case of significant overload, and particularly at 3T, there is a drop in the intensity of the hepatic signal, including the first echoes.
- The calculation of T2*/R2* may not be accurate, especially if the first TE is not short enough.

In this series at 3T, SIR method was more precise for these LIC > 200 µmol/g.

Thus, in case of high overload, especially at 3T, it is preferable to switch to the SIR method

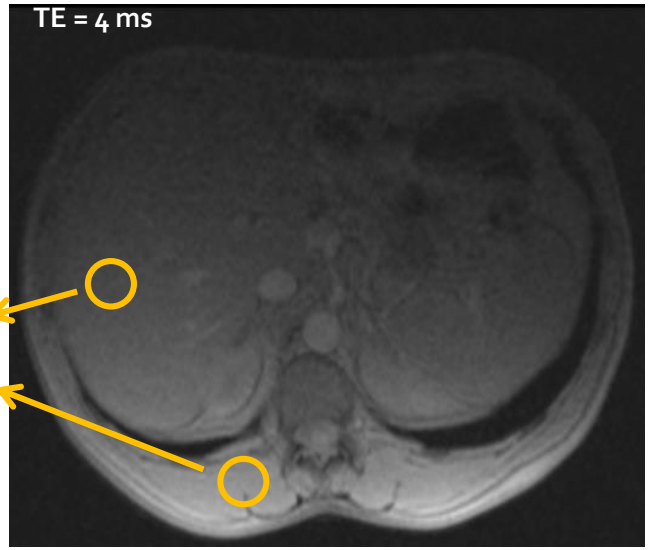


d'Assignies et al. Eur Radiol 2018.

SIR is not usable with surface coil

- As the SIR method compares the liver and muscle signal, the signal must be **homogeneous** within the entire image. Even if the signal distribution is corrected, the use of surface coil is not compatible with this method.
- Some devices (especially Siemens) can automatically select the bed **surface coils** if this option is not **unselected**.

In this case, the surface coils integrated in the MRI bed were used instead of the body coil integrated in the tunnel wall. There is a gradual decrease of the signal from the back to the front.

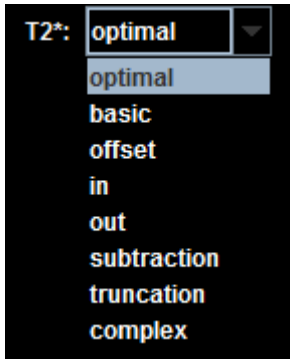


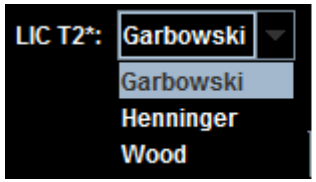
LIC = 180 instead of 10 µmol/g

Unselect the automatic selection of coils !
Check the signal homogeneity in the image !
Use MRQuantif which controls the coil used by analyzing the DICOM header

Don’t change the method in follow-up

- There are differences in results depending on the **method** and you should not change the method or parameters of the method in a follow-up.
- Our initial “SIR Gandon” method provides higher values than the T2* calculation or the “SIR Alustiza”. **At 1.5T, we do not recommend our method anymore**, but it remains available for patient follow-ups initially investigated by this method.
- There are also differences according to the **T2* calculation methods** (underestimation of T2* when calculating T2* after subtraction of background noise) and differences in the **formula converting R2* to LIC**.





Be aware of chosen method and parameters selection

Summary

- Quantification of liver iron by MRI is now more simple.
- If you have a 3D ME GRE dedicated MR sequence:
  - **AT 1.5T : LIC in µmol = R2*/2**
  - **But check that the result is coherent with the signal observed and don't trust values when there is a drop-off of liver signal on all echoes including the first ones.**
  - **Be careful at 3T, do a cross-check with SIR method.**
- Or use a 2D ME GRE dedicated MR sequence:
  - **We recommend to follow the mrquantif.org protocol which combines both methods and calculate simultaneously fat concentration.**
  - **It is also preferable to use the MRQuantif software, freely available, which controls acquisition parameters and simplify the process.**
  - **At 1.5T (not at 3T) the Rennes SIR method provides overestimated results. At that field, switch to the T2* calculation, except in case of follow-up with a previous result obtained with this method.**
- Never use SIR method when a surface coil was selected

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