Author's response to reviews

Title: Rapid T1 Quantification based on 3D Phase Sensitive Inversion Recovery

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Author's response to reviews: see over
Dear Editor,

The comments and suggestions of the referees were implemented in our manuscript. Point-by-point answers are provided in the following pages. Our manuscript has been uploaded in the correct format. Supplementary material is provided in the form of a copy of the manuscript where all changes are highlighted to assist the referees in reviewing the changes.

Thank you for handling our manuscript.

Yours sincerely,

J.B.M. Warntjes
Comments to the reviewers

Reviewer: Daniel Messroghli

- Major Compulsory Revisions
The phantoms used for this study consisted of water doped with a gadolinium-based contrast agent, with T1 between 283 and 749 ms. T2 times of phantoms of this type are typically nearly as long as T1, in contrast to in-vivo T2 values which are a lot shorter (e.g. ca. 50 ms for myocardium). Thus, signal behavior of such phantoms only gives a limited impression of the in-vivo situation, where the shorter T2 might affect the T1 measurements. For this reason, phantoms with short T2 (50 - 100 ms) are usually used for such analysis (e.g. based on agarose gel or CuSO4) and should be used to ensure that the measurements are valid.

We fully agree that the signal behaviour in phantoms never matches the in-vivo situation of the complex, multi-compartmental structure of living tissue where acquisition is further hampered by cardiac arrhythmia, movement and blood-flow. Hence all phantom studies have their limitations and are therefore designed to investigate particular aspects of the actual measurement where other variables are minimized.

In our case T1 relaxation was measured based on a spoiled gradient echo sequence. The observed signal S for each measured voxel corresponds to $S = f \cdot PD \cdot M \cdot \exp(-\frac{TE}{T_2^*}) \cdot \sin(a)$, where f is the scaling factor for the complete RF chain, including the coil sensitivity, PD is the proton density, M is the magnetization at the moment of acquisition, TE is the echo time, $T_2^*$ is the $T_2^*$ relaxation and a is the RF excitation flip angle. $T_1$ is essentially found using the ratio of two measurements with identical acquisition parameters, such that effectively the term $f \cdot PD \cdot \exp(-\frac{TE}{T_2^*}) \cdot \sin(a)$ is canceled. Therefore our T1 estimation does not depend on coil sensitivity, RF chain settings, tissue water content or $T_2^*$ relaxation.

Phantoms with a shorter $T_2$ then the ones we used will exhibit a slightly lower signal. The ratio between 2 identical measurements, however, entirely depends on the longitudinal magnetization behaviour since the transverse magnetization is spoiled. Therefore the results of such an exercise will be identical.

- Minor Essential Revisions
- 1) Methods, phantom measurements: the IR sequence for the assessment of nominal T1 values should use a longer TR (at least 5 x the longest T1 that is expected), e.g. 5000 ms.

Using inversion of 180 degrees and excitation of 90 degrees the observed signal behaviour of the IR sequence is proportional to $M_0^*(1 - 2 \cdot \exp(-\frac{T_{inv}}{T_1}) + \exp(-\frac{T_R}{T_1}))$. 


where the inversion delay $T_{\text{inv}}$ was varied while the repetition time $T_R$ was kept constant.

Indeed, conventionally $T_R$ is set to at least 5 times the longest $T_1$ to avoid a constant signal offset, proportional to $\exp(-T_R/T_1)$. In our case the longest $T_1$ was 750 ms which is indeed only a factor 4 compared with the $T_R$. Still, this offset affects the observed proton density (~1.8% too high) and not the observed T1 relaxation.

- 2) Methods, in-vivo measurements: contrast dose should be expressed as mmol/kg.
This has been changed

- 3) Results: The use of deltaR1 is misleading, since native R1 was not measured. What is the rationale of plotting deltaR1 of healthy myocardium vs. that of scarred myocardium (Fig. 8)? Why not plot R1 of the two over time?
Cardiac tissue has a baseline (native) $R_1$. Contrast media increases $R_1$ and hence must be expressed as the increase from baseline, i.e. $\Delta R_1$. Two references (8 and 9) were added to underline this and the text has been changed in various places to explain. Native $R_1$ was actually measured using our method and resulted in $R_1 = 1.2\pm0.2$ s$^{-1}$ for pre-Gd myocardium and $R_1 = 1.3\pm0.2$ s$^{-1}$ for the liver as stated in the text and in the figure headings. Since it is on the far end of the dynamic range the standard deviation is quite high but for the current study we deemed it was sufficient. Plotting $R_1$ over time for all 18 patients would definitely have been interesting but was not done due to time constraints for the MRI study in our hospital.

- 4) Discussion: The drawbacks of the technique should be discussed more openly:
- 24 heart beats is a very long breath-hold time for someone who is not healthy
It is indeed a long breath-hold, wording has been added to underline this.

- The technique is only suitable for post-contrast situations. Native T1 mapping is not possible with sufficient accuracy due to the short signal recovery times (2 $R_R$). This means that deltaR1 (representing partition coefficients) cannot be measured and thus fractional distribution volumes of contrast agents cannot be assessed, limiting the use of the technique e.g. for the assessment of diffuse myocardial fibrosis.
In this paper the focus was post-Gd measurement where the $T_1$ ranges in the order of 200-500 ms. For longer $T_1$ times indeed the used inversion delay of 300 ms is suboptimal, as can be seen in Fig. 3: At the highest measured $T_1=750$ ms the standard deviation is about 50 ms, corresponding to $R_1 = 1.3\pm0.1$ s$^{-1}$. For native $R_1$
measurements the natural choice of inversion delay would be higher, for example at 600 ms where the standard deviation at $T_1 = 750$ ms was only in the order of 10 ms (Fig. 3), corresponding to $R_1 = 1.33 \pm 0.02 \text{ s}^{-1}$. These results seem to suggest that the method may actually work for native $R_1$ as well, but this is pure speculation at this moment. Wording has been added to clarify this point.

The strength of the method is that the saturation effects are taken into account. Therefore the limitation of full relaxation is reduced allowing a fast $T_1$ measurement without full relaxation. This is clearly pictured in Fig. 4 where the dashed lines represent the $T_1$ estimation if saturation effects are ignored. These are completely wrong and should we have followed that path indeed native $T_1$ mapping would have been impossible. But we did perform the compensation, resulting in a consistent measurement of $T_1$ as depicted by the solid lines in Fig. 4. The only problem that arises with very long $T_1$'s is the increased sensitivity to noise.

- The susceptibility to heart rate variation is not so much a problem for $T_1$ accuracy of a given scan, but rather for comparability of $T_1$ between different scans (inter-study and inter-patient variability). This needs to be addressed since the main advantage of measuring $T_1$ is the possibility to compare the results between different groups of subjects.

Wording has been added to the introduction to underline this advantage.

- 5) Discussion, first paragraph: When discussing the influence of imperfect inversion it should be added that this might have to be considered when scanning is performed at higher field strength (3 T).

Wording has been added to the discussion to emphasize this.

- 6) Discussion: The section on multiple $T_1$ components within a single voxel might be discarded, since this issue is not specific to the new technique. It might not be specific but we felt it was worth mentioning a warning for the drawbacks of a 2-point method with respect to multi-compartment $T_1$ relaxation. This might be superfluous, but removal may lead to a decreased awareness or a sense of unsubstantiated optimism from our side. We hope that you can accept our concern.
Reviewer: Scott King

1) Title should reflect the need or advantage of this method. I suggest something like “Quantitative T1 Mapping Insensitive to RF Receive Coil Inhomogeneity using rapid 3D Phase Sensitive Inversion Recovery”
RF receive coil inhomogeneity limitations seem to vary across MR scanner vendors and highlighting this ‘selling point’ might weaken the manuscript for others, which makes us hesitate to alter the title at this late stage. But we agree that the RF receive coil inhomogeneity advantage of the method should have been mentioned earlier and it was moved to the introduction.

2) Background section, second paragraph is not strong. The authors really need to convince the reader that a quantitative T1 mapping is clinically useful.
Wording has been added to underline the advantages

2a) Move the statement “A variety of T1 mapping methods exist (see refs 11-15)” to right after the first line of the paragraph.
This paragraph was rewritten after the comments.

2b) First, if the authors could then make some statements about these existing methods that tell the reader that they do not allow the clinician to segment well and perform follow up studies on a different day with possibly different scanner settings. This would then justify the next statements the author has made as advantages of a quantitative method.
This paragraph was completely rewritten after the comments. Statements are made about existing methods. We tried to make a clean separation between the advantages of using T1 mapping and the advantage of this particular method.

2c) Second, the authors need to make some statements about why a 3D method is important since it appears to me that a 24 second breath-hold is too long for most patients. Because to me, since the method is for measuring T1 information during the “late enhancement” stage where there is plenty of time to image, a multiple 2D method may have been better since breath-hold times could then be lowered. The authors need to justify why the 3D method was used.
There are several disadvantages with a multiple 2D method. (1). The acquisition is performed at different, sequential times during the heart cycle, resulting in a discontinuous heart image throughout the volume, hampering a 3D segmentation process. (2). A M2D method has a lower SNR than a 3D method, effectively forcing an
even long breath-hold for sufficient image quality. That automatically leads to a multiple breath-hold strategy which potentially may have severe mis-registration issues. Our aim was a single breath-hold method, 3D seems the only option. The issue of the long 24 s breath-hold was taken up in the discussion.

2d) Thirdly, if it is true, the authors also need to state in this background section that existing methods are sensitive to inhomogeneity of receive coil sensitivity, and how this is a problem for accurate diagnosis which to me is a real problem, depending on the severity of the inhomogeneity, and could be a main advantage of this method. This is difficult to describe in a good way since we do not have numbers on how sensitive other methods are to inhomogeneity and therefore it would be unfair to say our method is better. The receive coil sensitivity issue has been moved up to the introduction and clearly stated as an advantage.

2e) Finally, follow up these statements stating that you have developed a rapid 3D quantitative T1 mapping method that is insensitive to receive coil inhomogeneity, which allows accurate segmentation of healthy myocardium and scar tissue even during follow up studies using different scanner settings. In summary of my comments regarding the background section, state all of the clinically relevant problems with the existing methods and then state that you have a new method that solves these problems!

Done!

3) page 11: The first mention of Fig.5 should describe what A-F are (healthy, fibrotic, fat etc)

This has been changed.

4) page 11: the statement “The relaxation rate of complete myocardium is estimated …” is confusing. What does “complete” mean? Maybe a different wording could be used here.

The text is rephrased.

5) page 11: Again, to some people, the fact that the dynamic curves look the same except for a shift in R1, between healthy and fibrotic tissue suggests that the dynamic information is not important but simply one data point would suffice,
say at 15 minutes. The authors could comment on this.

The dynamic information might hold important clues. Contrast media concentration is expected to scale with $\Delta R_1$, the increase of $R_1$ above the baseline $R_1$. Looking at Fig. 6 we see that fibrotic myocardium (e.g. curve D) shows a decrease of $R_1 = 5.8$ to $3.6$ s$^{-1}$, corresponding to a reduction of $\Delta R_1$ of $(3.6-1.2)/(5.8-1.2) = 52\%$ whereas healthy myocardium (e.g. curve B) shows a reduction of $(2.2-1.2)/(4.4-1.2) = 31\%$, indicating much faster wash-out kinetics and therefore a sign of different perfusion characteristics.

Comments are added to the text

6) page 11: “According to Fig.6 hyper-enhancement of fibrotic tissue is already present after 5 minutes and slowly increases during the following 30 minutes”. Are you drawing attention to the difference between healthy and fibrotic tissue or the fibrotic tissue alone? Because a similar statement could be made regarding the healthy tissue. Please re-phrase.

This is rephrased, it was commenting fibrotic compared to healthy.

7) page 14: The statement “Actins to minimize … , might decrease the image quality” is poorly stated. These are two very important points that should be made separately. The authors could state that without a quantitative T1 method, fat suppression techniques may need to be employed and then state a few negative effects of having to include fat suppression. This also might be added as a “need” in the background section! A separate statement should be used about having to use a uniform receive coil sensitivity such as a body coil, that would mean lower SNR and thus lower quality images; but this should be stated right after the statements regarding RF coil sensitivity.

These points are addressed, the relevant texts have been updated

8) The conclusions are weak. The authors could strengthen the conclusions by re-stating that a quantitative T1 mapping method was developed that allows accurate segmentation during follow up studies, that is insensitive the receive coil inhomogeneity and therefore, phased array coils with high SNR can be employed, and does not require fat suppression for correct interpretation of infarct area.

The conclusions are rephrased.

Minor Essential Revisions:
1) page 6: Equation 8, I think “expTC” should be replaced with “exp(TC)”
Done.

2) page 7: “Prerequisite, however, …” should be changed to “A prerequisite, however, …”
Done.

3) page 14: remove the word “resulting” from the statement “The resulting bright fat signal in the LGE images may lead to an incorrect interpretation of the size of the infarct area”, as this suggests that the bright fat signal is a result of the previous statement on coil sensitivity, which I don’t think is the intention.
This text has been rephrased

4) page 15: “The ability to synthetically vary Tinv after the actual may …” is confusing. After the actual what? Please re-word.
The word ‘acquisition’ was missing.

5) Page 17: Reference #7 is incorrect. The journal is Magn Reson Med
This is corrected.

Discretionary Revisions:
1) page 5, Explain why “A low k-space profile order ensures that the image intensity is not altered due to differences in MB …”
In MRI the image intensity is coded mainly by the lower k-space lines and the details mainly by the higher k-spaces lines. To ensure that the image intensity of the two measurements reflect mainly the magnetization $M_B$ and $M_D$ (and not a value in between $M_B$ and $M_C$ or $M_D$ and $M_E$, respectively) a low to high k-space line ordering is applied during the acquisition. The text has been rephrased for clarity.

2) page 10: It might be useful to the reader if you comment on why the error bars are larger for longer T1.
Text is added.

3) Page 10: Please site a reference or explain the particular use of the Monte Carlo simulation
Text has been rephrased to explain.

4) Fig.5: The boxes are hard to see in the color figure, but ok in the grayscale version when printed.
The boxes are made sharper to ensure a good quality both in color and BW.

5) Fig. 6,7: It would have been really nice to see time zero prior to gadolinium on the graph.
That is the baseline $R_1$ as indicated by the dashed line at 1.2 and 1.3 s$^{-1}$, respectively.

6) Fig.5-7: Generally I got confused looking at Fig.5 which is a T1 map, and then looking at Fig.6,7 which are reciprocal R1 maps. The authors could include a R1 map in addition to the T1 map.
A very good point and a difficulty for us to convey our message. Generally ‘$T_1$’ is used in text books explaining MRI and therefore we chose to go through the theory, methods and results using ‘$T_1$’ as the main term. For the dynamic behavior of longitudinal relaxation in tissue due to contrast media it is, however, more appropriate to use ‘$R_1$’ instead, resulting in a potential confusion caused by the switch of terminology in our manuscript. The text has been rephrased in some places to indicate more clearly where switches are made.

7) page 12: Explain why “the difference in standard deviation which the LL method is 2-3 times that of the proposed methods”, it is not clear why this is the case.
Text is added, the LL was a single slice, leading to lower SNR.
Reviewer: Tom CC Hu

Specific Comments/Questions:
1 Abstract, Methods, Page 2 – “...healthy and fibrotic myocardium was measured at about 15 minutes post-contrast.” Would the 15 minutes post-contrast time period provide the optimal contrast delayed-enhancement? Please elaborate.
It is generally accepted that after 10-15 minutes a clear late enhancement effect is present. This is also shown in Fig. 6 where the difference of curves A and B compared to C and D is large at 15 minutes. To state that this is optimal is impossible to substantiate, it depends on the patient’s physiology, illness and weight, as well as the contrast dose. Fig. 6 even suggests that a longer waiting period would increase the difference in $R_1$ between healthy and fibrotic tissue but this might be sub-optimal concerning the time a patient needs to spend in the scanner. We were not sure on what we could elaborate here to strengthen the method.

2 Background, Page 3 – “Quantification of the absolute T1 relaxation provides a measure for absolute local contrast media concentration.” How would one be able to calibrate the contrast media concentration in the clinical situation? Please elaborate.
This would be very difficult since so many parameters are involved. Possibly a phantom study on myocardial tissue in a bath of Gd doped water at 37 degrees would be indicative. Text was rephrased to indicate that this is possible but was not done. Furthermore 2 references are added with more background information.

3 Background, Page 5 – “A perfect inversion pulse is assumed, a small deviation of the complete inversion has only a negligible effect on the calculations.” How much would this small deviation effect the final T1 estimation? How much would the difference make in terms of healthy versus infracted myocardium post-contrast media? Please elaborate.
Text was added with an estimation of the error. A reduction of the flip angle to 90% of the original (162 degrees rather than a full 180 degrees) would lead to an overestimation of T1 of 2-3%.

4 Methods, Page 8 – “For the in-vivo measurements the Tinív was by default set to 300 ms and the flip angle to 18 degrees.” Would this be much differ between the infracted and healthy myocardium? Would one be able to further optimize the
Tinv due to infarcted myocardium? Any potential incomplete recovery from the 18 degrees flip angle?

The choice of 300 ms Tinv and 18 degrees excitation flip angle was made since this provides a good estimation of T_1 in the range 200-500 ms at normal heart rates. Both healthy and infarcted myocardium exhibit values in this range post-Gd.

5 Results, Page 11-12 – “…although the LL results in slightly lower R1 values.” What are the potential explanations for this difference?

Probably a pulse profile effect where the effective flip angle of the slice-selective pulse was less than expected. Text has been added to clarify.

6 Discussion, Page 13 – “…Fig. 4 shows that small changes in heart rate have less influence on the typical T1 values than the noise level of the measurement.” How much is the T1 variation due to irregular heart rate (R-R)? Please elaborate.

Text is added to the discussion.