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# Rapid $T_1$ quantification based on 3D phase sensitive inversion recovery

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## Abstract

**Background:** In Contrast Enhanced Magnetic Resonance Imaging fibrotic myocardium can be distinguished from healthy tissue using the difference in the longitudinal  $T_1$  relaxation after administration of Gadolinium, the so-called Late Gd Enhancement. The purpose of this work was to measure the myocardial absolute  $T_1$  post-Gd from a single breath-hold 3D Phase Sensitivity Inversion Recovery sequence (PSIR). Equations were derived to take the acquisition and saturation effects on the magnetization into account.

**Methods:** The accuracy of the method was investigated on phantoms and using simulations. The method was applied to a group of patients with suspected myocardial infarction where the absolute difference in relaxation of healthy and fibrotic myocardium was measured at about 15 minutes post-contrast. The evolution of the absolute  $R_1$  relaxation rate ( $1/T_1$ ) over time after contrast injection was followed for one patient and compared to  $T_1$  mapping using Look-Locker. Based on the  $T_1$  maps synthetic LGE images were reconstructed and compared to the conventional LGE images.

**Results:** The fitting algorithm is robust against variation in acquisition flip angle, the inversion delay time and cardiac arrhythmia. The observed relaxation rate of the myocardium is  $1.2 \text{ s}^{-1}$ , increasing to  $6 - 7 \text{ s}^{-1}$  after contrast injection and decreasing to  $2 - 2.5 \text{ s}^{-1}$  for healthy myocardium and to  $3.5 - 4 \text{ s}^{-1}$  for fibrotic myocardium. Synthesized images based on the  $T_1$  maps correspond very well to actual LGE images.

**Conclusions:** The method provides a robust quantification of post-Gd  $T_1$  relaxation for a complete cardiac volume within a single breath-hold.

## Background

Contrast Enhanced Magnetic Resonance Imaging (CEMRI) is the preferred modality for the detection and characterization of myocardial viability [1-6]. At 10-30 minutes after the administration of a  $T_1$  contrast medium fibrotic or otherwise damaged myocardium exhibits hyper-enhancement in comparison with healthy tissue, owing to differences in wash-out kinetics of the contrast agent. Typically, a Phase Sensitive Inversion Recovery (PSIR) sequence is applied for high image contrast between healthy and fibrotic myocardium. In such an acquisition an inversion pulse is applied followed by two acquisitions, one at a short inversion delay time  $T_{inv}$  and a second during the same heart phase at the subsequent heart beat. The total kernel time of the acquisition

spans two cardiac RR intervals. The latter acquisition is used to correct the background phase of the former such that a real image is reconstructed instead of a modulus. The advantage of this procedure is that there is no contrast degradation due to signal rectification of the original modulus image [7].

The contrast in the PSIR image is governed by the longitudinal  $T_1$  relaxation of the various tissues. Signal intensity differences in the images indicate differences in  $T_1$  but, since the image is arbitrarily scaled, no absolute numbers can be retrieved. Changes in the absolute relaxation rate  $R_1$  ( $= 1/T_1$ ) provides a measure for absolute local contrast media concentration [8,9]. Monitoring  $R_1$  over time pictures the actual contrast medium dynamics without the potential offset intensity bias or changes caused by heart rate variability, as seen with conventional dynamic  $T_1$ -weighted imaging. Quantification may even improve the stability of segmentation of healthy myocardium and scar tissue. Especially in

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follow-up studies on the volume of the myocardium and scar, a reliable segmentation is required, independent of scanner settings [10-12]. Finally,  $T_1$  maps are independent of RF coil sensitivity. This may be important for imaging using (phased array) coils with a strong spatial sensitivity gradient and without proper intensity scaling (such as CLEAR, Constant Level Appearing). It may also reduce the need for a fat suppression technique to remove the high-intensity fat signal that may disturb the image reading. A variety of  $T_1$  mapping methods exists (see e.g. Refs. [13-17]). A number of these methods rely on strategies with continuous acquisition, which leads to movement artifacts for the heart. Others require several breath-holds to cover the complete cardiac volume. In this work a method is described to retrieve the absolute  $T_1$  relaxation based on a 3D PSIR acquisition, which can cover the complete cardiac volume within a single breath hold.

### Theory

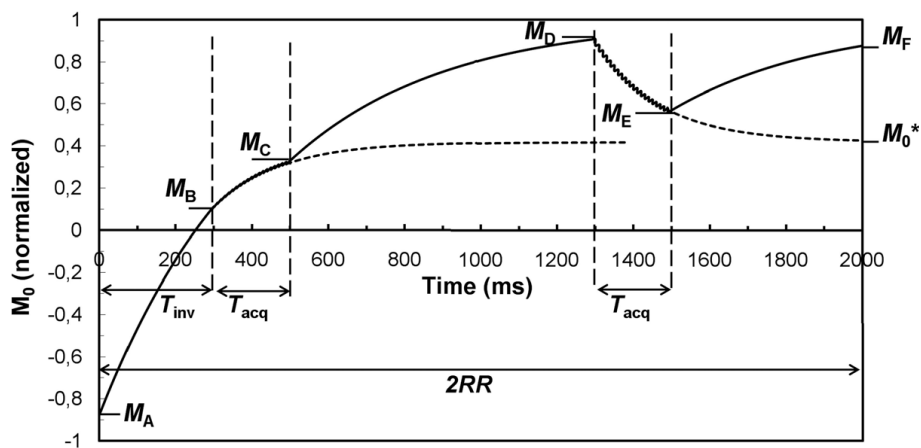
The evolution of the spin magnetization during a 3D PSIR sequence as a function of time is graphically described in Fig. 1. The fully relaxed magnetization  $M_0$  is normalized to 1. The measurement is repeated every two cardiac RR intervals, where RR is set to 1 s for Fig. 1. To estimate  $T_1$  properly, saturation and acquisition effects on the magnetization must be taken into account. The magnetization starts at a certain steady-state magnetization  $M_A$  after the inversion pulse and relaxes with  $T_1$  during the inversion delay time  $T_{inv}$

towards  $M_B$ . During the acquisition time  $T_{acq}$  the magnetization evolves under both  $T_1$  relaxation and the continuous application of the RF flip angles  $\alpha$  in combination with the subsequent spoiling of the signal, repeated every repetition time TR. This causes a shorter, apparent  $T_1^*$  relaxation towards a saturated magnetization  $M_0^*$  as long as the acquisition time  $T_{acq}$  continues [18,19]. The  $T_1^*$  and  $M_0^*$  can be found with:

$$\frac{M_0^*}{M_0} = \frac{T_1^*}{T_1} = \frac{TR}{TR - T_1 \ln(\cos \alpha)} \quad (1)$$

The flip angle  $\alpha$  is assumed to be perfect for Eq. 1. It may deviate somewhat due to an imperfect RF slab selection profile and the  $B_1$  inhomogeneity but since the  $T_{acq}$  is short compared to the total RR interval the effect of a deviation on the following equations is small. After the first acquisition the magnetization relaxes again with  $T_1$  from  $M_C$  towards  $M_D$  where the second acquisition starts. In contrast to the original PSIR measurement identical scanning parameters are applied for the two acquisitions because both are equally important for the  $T_1$  quantification. The magnetization after the second acquisition,  $M_E$ , relaxes with  $T_1$  towards the magnetization  $M_F$  at 2RR, just before the subsequent inversion pulse. The total magnetization evolution is thus described by:

$$M_B = M_0 - (M_0 - M_A) \exp(-T_{inv} / T_1) \quad (2)$$



**Figure 1 Schematic representation of the evolution of the magnetization during a 3D PSIR acquisition.** The magnetization evolution is depicted of a tissue with  $T_1 = 400$  ms and an RR interval of 1 s. The steady state magnetization  $M_A$ , just after the inversion pulse, relaxes during the inversion delay  $T_{inv}$  towards  $M_B$  where the first acquisition starts with a time  $T_{acq}$ . The magnetization is allowed to relax again until the second acquisition at  $M_D$ . Finally the magnetization relaxes towards  $M_F$ , just before the subsequent inversion pulse. During the acquisition periods the magnetization approaches the saturated magnetization  $M_0^*$  with an effective relaxation time  $T_1^*$  (indicated by the dashed lines), depending on the repetition time TR (10 ms) and the applied flip angle  $\alpha$  ( $15^\circ$ ). The acquisition time has a duration of  $n$  time TR where the TFE factor  $n = 19$  in this example.

$$M_C = M_0^* - (M_0^* - M_B) \exp(-T_{acq} / T_1^*) \quad (3)$$

$$M_D = M_0 - (M_0 - M_C) \exp(-(T_{RR} - T_{acq}) / T_1) \quad (4)$$

$$M_E = M_0^* - (M_0^* - M_D) \exp(-T_{acq} / T_1^*) \quad (5)$$

$$M_F = M_0 - (M_0 - M_E) \exp(-(T_{RR} - T_{acq} - T_{inv}) / T_1) \quad (6)$$

A perfect inversion pulse is assumed, a small deviation of the complete inversion has only a negligible effect on the calculations. Typically, a 10% reduction of the inversion angle (162 degrees rather than 180) results in an overestimation of 2-3% for a  $T_1$  in the range 200-800 ms. For a single shot PSIR acquisition, with sufficient time between subsequent measurements for the magnetization to fully recover,  $M_A$  equals  $-M_0$ . For a multi-shot acquisition, either a multi-slice or a 3D sequence, where an inversion pulse is applied every 2RR, in clinical practice a steady-state is reached where  $M_A = -M_F$  and  $(-M_A) < M_0$ .

Since Eqs. 1-6 are coupled equations there are in fact only 2 unknown parameters,  $M_0$  and  $T_1$ , and all 6 magnetizations  $M_{A-F}$  are defined if two of them are known, in case of the 3D PSIR measurement  $M_B$  and  $M_D$ . A low-high k-space profile order ensures that the image intensity reflects the magnetization in  $M_B$  and  $M_D$  even though the magnetization changes during the acquisition. The value for  $T_1$  cannot explicitly be calculated and  $M_0$  and  $T_1$  are found using an iterative process. To start the iteration  $M_0$  and  $-M_A$  are assumed to be equal to  $M_D$ . Using Eq. 2 a coarse  $T_1$  can be calculated according to

$$T_1 = \frac{-T_{inv}}{\ln\left(\frac{M_D - M_B}{2M_D}\right)} \quad (7)$$

Using this  $T_1$  in Eq. 3  $M_C$  is calculated. A new  $M_0$  is then estimated rewriting Eq. 4 as

$$M_0 = \frac{M_D - M_C \exp(TC)}{1 - \exp(TC)} \quad (8)$$

where  $\exp(TC)$  equals  $\exp(-(T_{RR} - T_{acq})/T_1)$ . Finally  $M_F$  is calculated using the new  $M_0$  in Eqs. 5 and 6. The second iteration starts with the estimated  $M_0$  from Eq. 8 and a new  $M_A = -M_F$ .

The proposed method is compared to the Look-Locker (LL) sequence [20]. This method can be

described as a special case using the same equations. The acquisition is then continuous such that  $M_A = M_B$ ,  $M_C = M_D$  and  $M_E = M_F$  and the evolution of the magnetization is in fact described by Eqs. 3 and 5 only. This set of 2 equations can be solved. The steady-state magnetization  $M_t$  as a function of time  $t$  after the inversion pulse is (if the inversion is repeated every RR interval) given by:

$$M_t = M_0^* - \left( \frac{2M_0^*}{1 + \exp(-T_{RR} / T_1^*)} \right) \exp(-t / T_1^*) \quad (9)$$

Using Eq. 9 the  $T_1^*$  relaxation can be retrieved from a LL sequence. Subsequently the actual  $T_1$  can be calculated using Eq. 1. From these equations it can directly be seen that the intensity zero-crossing of a LL sequence, in general, does not coincide with the intensity zero-crossing of a PSIR sequence. The continuous acquisition of a LL leads to a  $T_1^*$  relaxation which is shorter than  $T_1$  and the saturation and acquisition effects lead to a different steady-state magnetization. Therefore care should be taken in using the LL to find the intensity zero-crossing for another sequence, although this is commonly done.

As an additional confirmation of the accuracy of the  $T_1$  quantification the approach of Synthetic MRI [21-24] is applied: The  $T_1$  maps are used as input to simulate a 3D spoiled gradient echo sequence (Inversion Recovery Turbo Field Echo or IR-TFE). Based on the  $T_1$  values of the quantification scan the expected image intensity of an IR-TFE can be calculated for any chosen  $T_{inv}$  using Eqs. 1-6 (using  $M_D = M_E$  and a kernel time of a single RR). The synthesized images are compared with the actual ones with the same  $T_{inv}$ . The IR-TFE is interesting since this sequence does not have the second acquisition, like the PSIR method, to restore phase and hence potentially has up to 41% more SNR within the same scan time compared to a PSIR sequence of equal geometry. A prerequisite, however, is that the optimal inversion delay is applied since the IR-TFE scans do suffer from signal rectification in case  $T_{inv}$  is chosen too short [25]. To ensure an optimal  $T_{inv}$  the synthetic images can be set first such that the healthy myocardium appears black. Subsequently this value for  $T_{inv}$  can be used as input for the actual IR-TFE scan.

## Methods

### Phantom measurements

All experiments were performed on a 1.5T Achieva scanner (Philips Healthcare, Best, The Netherlands). Phantoms were made that matched the relevant cardiac relaxation rates as good as possible. Water was used with a 2.5% Agerose solution (Sigma-Aldrich, St. Liouis,

USA) and different concentrations of the Gadolinium contrast agent (Magnevist, 0.5 mmol/mL, Bayer Healthcare, Germany, diluted to 0.06 - 0.3 mmol/L) resulting in  $T_1 = 228, 298, 411, 539, 638$  and  $754$  ms. The  $T_2$  relaxation times of all phantoms was in the range 42-59 ms. The 3D PSIR protocol for the  $T_1$  quantification was a segmented 3D Turbo Field Echo Planar Imaging (TFEPI) sequence with an EPI factor 3 and a TFE factor 23. The echo time (TE) was 4.2 ms and the repetition time (TR) 9.4 ms leading to an acquisition phase of 215 ms per heart beat. The matrix size was  $228 \times 138$  (reconstructed  $320 \times 320$ ) over a Field of View (FOV) of  $350 \times 320$  mm. The slices had a thickness of 5 mm (overcontiguous, i.e. the slices overlap). Using a Sense factor 2 a volume of 12-18 slices can be acquired within 24 seconds, depending on the heart rate (2 heart beats per slice). For the phantoms physiology simulation was used for artificial heart triggering. A heart rate of 60 beats per minutes was set, resulting in 12 slices in 24 seconds.

The absolute  $T_1$  relaxation time of the phantoms was validated using a standard inversion recovery sequence with 9 separate measurements at an inversion delay time of 50, 100, 150, 200, 250, 300, 500, 1000 and 2900 ms. The TE was 29 ms (EPI factor 13), TR = 3000 ms and the flip angle  $90^\circ$ .

#### In-vivo measurements

For the in-vivo measurements the  $T_{inv}$  was by default set to 300 ms and the flip angle to 18 degrees. The acquisition was performed during diastole. The number of slices was adjusted in the range 12-18 slices to fit within a 24 seconds breath-hold. The quantification method was added to routine clinical examinations of patients that were followed up after primary PCI for ST-elevation myocardial infarction. The study was approved by the regional ethics committee and complied with the declaration of Helsinki. All patients gave written informed consent. They were given 0.2 mmol/kg (max. 15 mmol) Gadolinium contrast agent (Magnevist 0.5 mmol/ml, Bayer Healthcare, Germany). On one patient, the  $T_1$  quantification protocol was performed every 2 minutes. The quantification scan was interleaved with a LL sequence, a single slice inversion recovery scan with a flip angle of 15 degrees and a TR of 25 ms. The LL resulted in 29 heart phases within a breath-hold of 17 seconds. The matrix size was  $228 \times 201$ , reconstructed to  $320 \times 320$ .

On all other patients the quantification method was applied once, about 15 minutes after contrast injection. The Synthetic MRI approach was used to establish the optimal inversion delay. Directly after the 3D PSIR acquisition the images were sent to the PACS system (IDS5, Sectra Imtec, Sweden) where the optimal inversion delay time was retrieved from the synthetic images

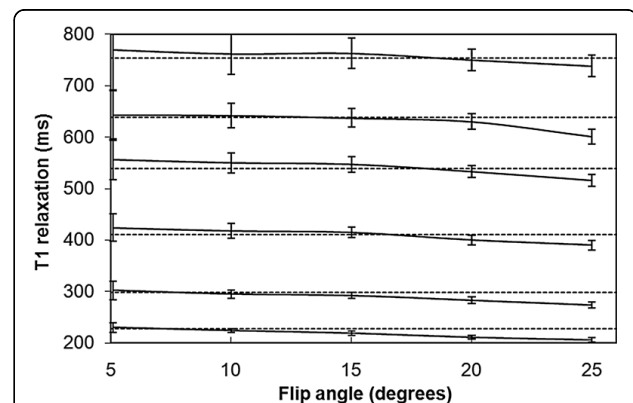
using a dedicated cardiac package (SyMRI Cardiac Studio, SyntheticMR AB, Sweden). The value for the optimal  $T_{inv}$  was used as input for the IR-TFE sequence to ensure black myocardium for this protocol. To compensate for the time delay between the 3D PSIR and the IR-TFE, in general about 1 minute, 20 ms was added to the suggested  $T_{inv}$ .

The IR-TFE sequence was a segmented 3D spoiled gradient echo sequence with TE = 1.3 ms, TR = 4.4 ms and TFE factor 43, leading to an acquisition phase time of 188 ms, also acquired during diastole. In total 17 slices were acquired with a thickness of 5 mm (overcontiguous) and Sense factor 2. The matrix size was  $256 \times 172$  (reconstructed to  $320 \times 320$ ) over a FOV of 350 mm resulting in a scan time of 17 heart beats.

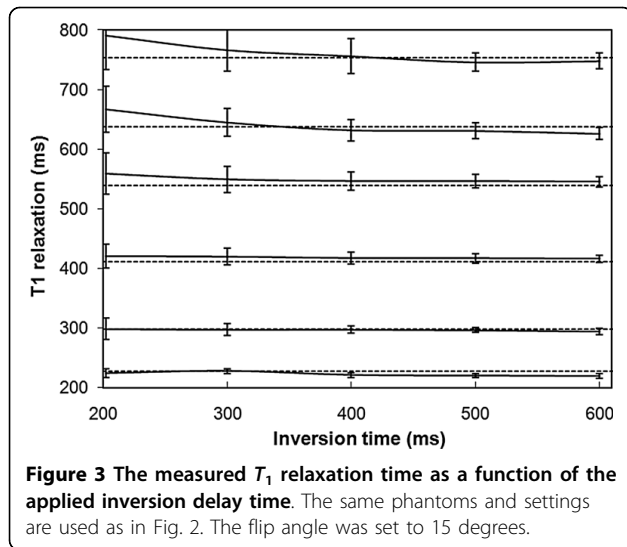
#### Results

The measured  $T_1$  relaxation time of various phantoms as a function of the applied acquisition flip angle is shown in Fig. 2 where the  $T_{inv}$  is set to 300 ms. The estimation of the  $T_1$  relaxation is consistent over a large range of applied flip angles. The only exception is the combination of long  $T_1$  and high flip angle when the  $T_1$  time is underestimated. In Fig. 2, the  $T_1$  relaxation time as measured with the standard inversion recovery is displayed as the dotted lines. The standard deviation of  $T_1$  over 100 pixels is shown as the error bars. Based on Fig. 2 the optimal flip angle of the proposed method is in the range 15-20 degrees, with high SNR and good agreement with the standard method.

Fig. 3 exhibits the measured  $T_1$  relaxation time of these phantoms as a function of the applied inversion delay time where the flip angle is set to 15 degrees.



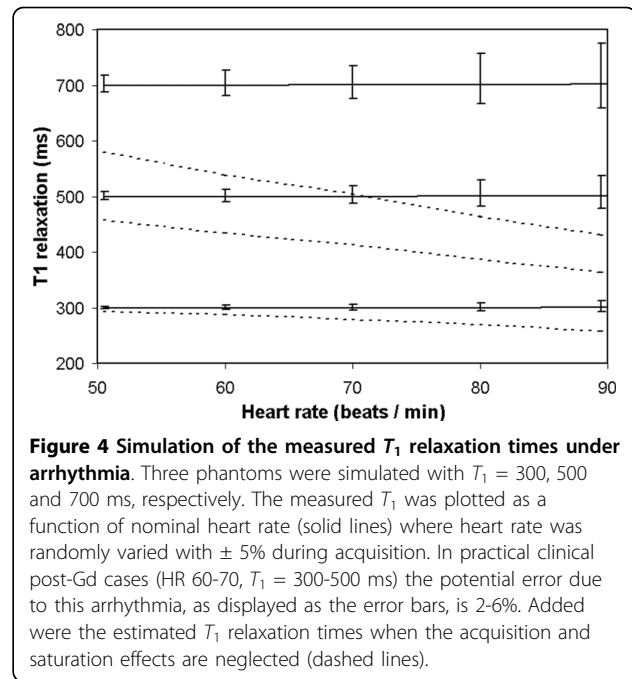
**Figure 2** The measured  $T_1$  relaxation time of various phantoms function of the applied flip angle  $\alpha$ . Six phantoms are shown with different  $T_1$  contrast medium concentration. The inversion delay is 300 ms. For comparison the dashed lines are shown, which represent the  $T_1$  relaxation time as measured with standard inversion recovery. The error bars are the standard deviation of the measurement over 100 pixels.



**Figure 3** The measured  $T_1$  relaxation time as a function of the applied inversion delay time. The same phantoms and settings are used as in Fig. 2. The flip angle was set to 15 degrees.

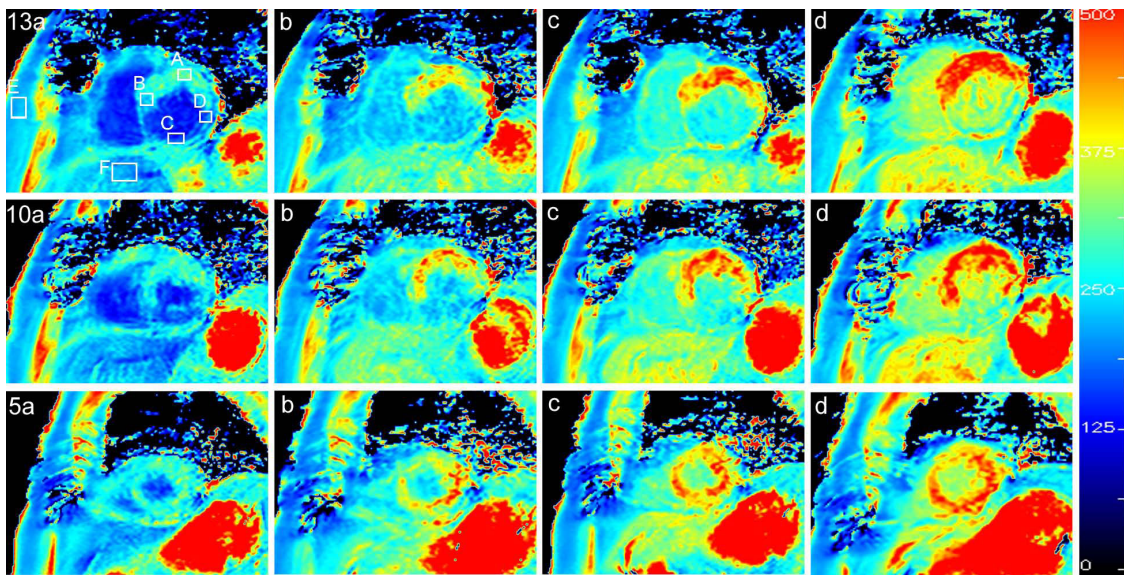
A consistent measurement of  $T_1$  is achieved over a large range of applied inversion delays. The combination of very short inversion delay times and high  $T_1$  values may cause an overestimation of the  $T_1$  relaxation time. This is possibly explained in part by the increased Gibbs' ringing at the phantom edges due to the high signal intensity difference. Fig. 3 shows that the inversion delay can be set anywhere in the range of 300 - 600 ms for  $T_1$  values in the range of 200 - 800 ms.

Based on Figs. 2 and 3 the flip angle was set to 18 degrees and the inversion delay time to 300 ms for the post-Gd *in-vivo* measurements. A Monte Carlo simulation was performed with this setting to monitor the potential error of the fitting due to cardiac arrhythmia. The magnetization was calculated using Eqs. 2-6 while the heart rate was varied randomly for each RR-interval in the range  $\pm 5\%$  during the acquisition. In Fig. 4 the estimation of three different  $T_1$  values (300, 500 and 700 ms) at nominal heart rates is displayed. The error bars indicate the standard deviation caused by the random heart rate. The error in  $T_1$  is smaller than  $\pm 4\%$  for 300 ms and smaller than 7% for 500 ms over the entire range of heart rates between 60 and 90 beats per minute. At high  $T_1$  values and high heart rates the error becomes larger, up to 10% for  $T_1 = 700$  ms and a heart rate of 90 bpm. To clarify the importance of taking the actual magnetization behaviour during the sequence into account, the estimated  $T_1$  is shown neglecting the influence of the acquisition and the steady-state saturation effects on the magnetization (Fig 4, dashed lines). The  $T_1$  values are severely underestimated at higher heart-rates. The effects may only be neglected if the RR interval equals more than 4 - 5 times the value of  $T_1$ . This occurs only at clinically irrelevant low heart rates.



**Figure 4** Simulation of the measured  $T_1$  relaxation times under arrhythmia. Three phantoms were simulated with  $T_1 = 300, 500$  and  $700$  ms, respectively. The measured  $T_1$  was plotted as a function of nominal heart rate (solid lines) where heart rate was randomly varied with  $\pm 5\%$  during acquisition. In practical clinical post-Gd cases (HR 60-70,  $T_1 = 300-500$  ms) the potential error due to this arrhythmia, as displayed as the error bars, is 2-6%. Added were the estimated  $T_1$  relaxation times when the acquisition and saturation effects are neglected (dashed lines).

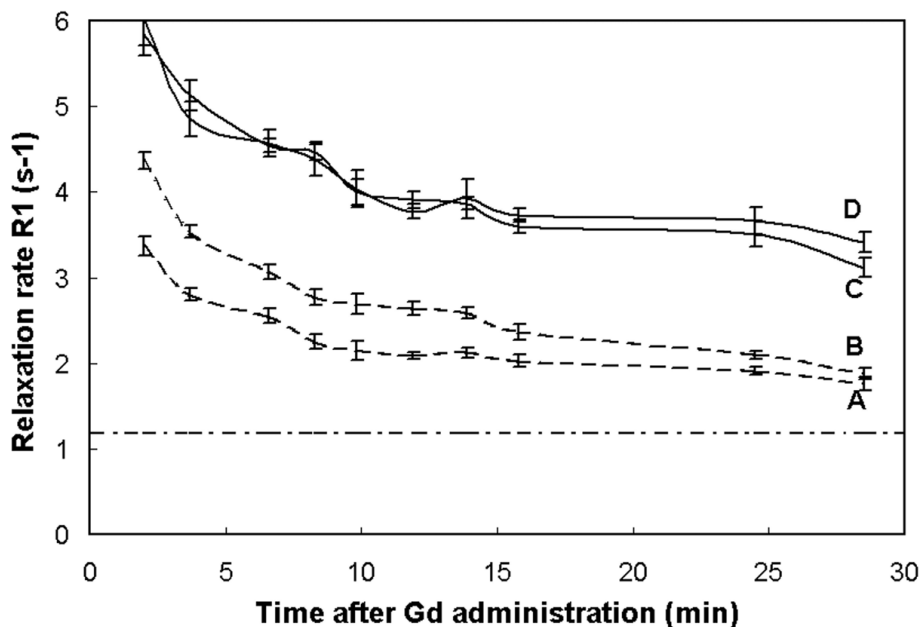
An example of the measured absolute  $T_1$  maps of a short axis slice of a patient with fibrotic myocardium is shown in Fig. 5. The color scale ranges from 0 to 500 ms. Three slices are shown of the 17 that were acquired in the 3D volume (slice number 13, 10 and 5) at various times after the administration of Gd. A clear difference can be seen between the healthy myocardium and the fibrotic myocardium in slices 13 and 10. Six Regions of Interest (ROI) were placed in the images, as displayed in slice 13a, to monitor the relaxation rate  $R_1$  ( $1/T_1$ ) as a function of time after the Gd injection, where A and B were positioned in healthy myocardium, C and D in fibrotic myocardium, E in the subcutaneous fat and F in the liver. In Fig. 6 the data of the ROIs A-D are shown. The relaxation rate of all myocardial tissue is estimated to be in the order of  $6 - 7 \text{ s}^{-1}$  directly after the Gd administration. It rapidly decreases for healthy tissue and at 10-15 minutes post-Gd  $R_1$  is relatively flat at  $2 - 2.5 \text{ s}^{-1}$ . The  $R_1$  of fibrotic tissue, on the other hand, remains high at  $3.5 - 4 \text{ s}^{-1}$ . The dashed-dotted line is the reference  $R_1 = 1.2 \pm 0.2 \text{ s}^{-1}$  for myocardium as measured with our method before the Gd administration. According to Fig. 6 the higher relaxation rate (and hence the hyper-enhancement) of fibrotic tissue compared to healthy tissue is already present after 5 minutes and the difference slowly increases during the following 25 minutes. During this interval the  $\Delta R_1$  above the baseline  $R_1$  reduces to about 30% for curves A and B whereas it is only to 50% for curves C and D, indicating faster wash-out kinetics for healthy myocardium. A Look-Locker sequence was applied as well, interleaved



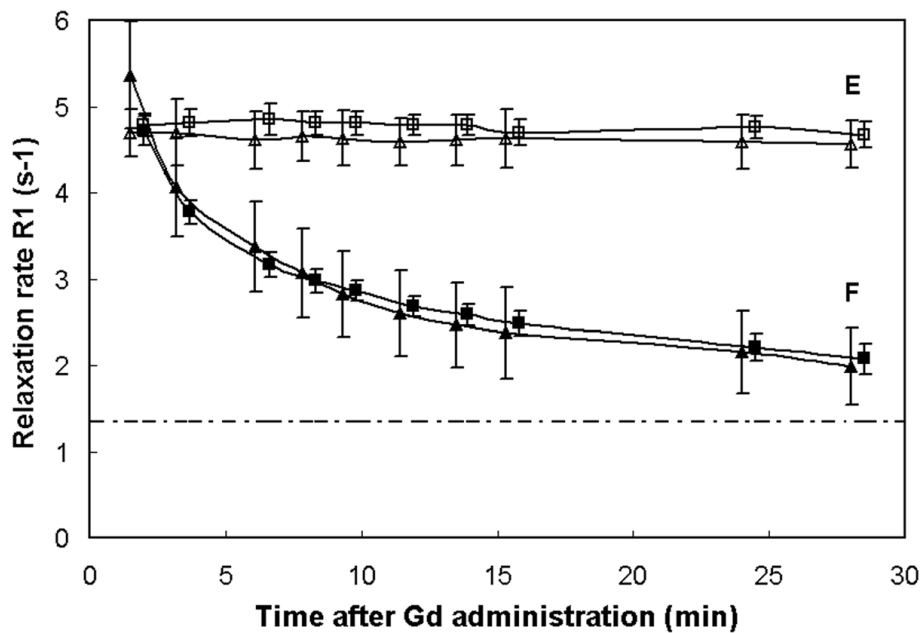
**Figure 5** The absolute  $T_1$  relaxation maps of three short axis slices of the heart. The slice numbers 13, 10 and 5 out of the 17 that were acquired in a scan time of 19 seconds are shown. The color scale is in the range 0-500 ms. The time after the administration of Gadolinium was **a)** 2 min., **b)** 6 min., **c)** 12 min and **d)** 24 min. Indicated in slice 13a are the Regions of Interest that are plotted in the following figures.

between the acquisitions for the proposed new method. This measurement obtained a single slice which was matched geometrically to slice 13 of our method. Since LL is acquired over the complete cardiac cycle direct fitting of  $T_1$  relaxation leads to severe motion artifacts in

the region of the heart. The LL measurement is compared with our method for the subcutaneous fat (ROI E in Fig. 5) and for the liver (ROI F), that remain relatively still. As can be seen from Fig. 7, the two methods agree excellently, although the LL results in slightly lower  $R_1$



**Figure 6** The absolute relaxation rate  $R_1$  as a function of time for cardiac tissue. The  $R_1$  as a function of time after Gd administration is shown for the 4 ROIs A, B, C and D, as indicated in slice 13a in Fig. 5. Both A and B are positioned in healthy myocardium, C and D are positioned in fibrotic myocardium. The error bars indicate the standard deviation inside the ROI of  $\sim 100$  pixels. The dashed-dotted line is the reference  $R_1 = 1.2 \pm 0.2 \text{ s}^{-1}$  of myocardium, obtained before Gd injection.



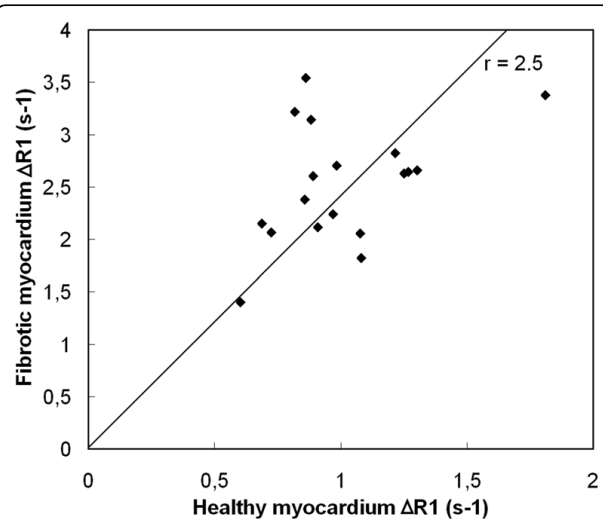
**Figure 7** The absolute relaxation rate  $R_1$  as a function of time for liver tissue and fat. The  $R_1$  as a function of time after Gd administration is shown for the 2 ROI's E and F, as indicated in slice 13a in Fig. 5. The proposed method (squares) is compared to the Look-Locker method (triangles). ROI E is positioned in subcutaneous fat (open labels), ROI F is positioned on the liver (filled labels). Fat has a stable  $R_1 = 4.8 \pm 0.1 \text{ s}^{-1}$  while the relaxation rate of the liver decreases towards the dashed-dotted line which is the reference  $R_1 = 1.3 \pm 0.2 \text{ s}^{-1}$ , obtained by our method before Gd injection. The Look-Locker method obtained a reference liver  $R_1 = 1.3 \pm 0.4 \text{ s}^{-1}$ .

values, probably due to an imperfect pulse-profile. Note also the difference in standard deviation which for the (single-slice) LL method is 2-3 times that of the proposed method.

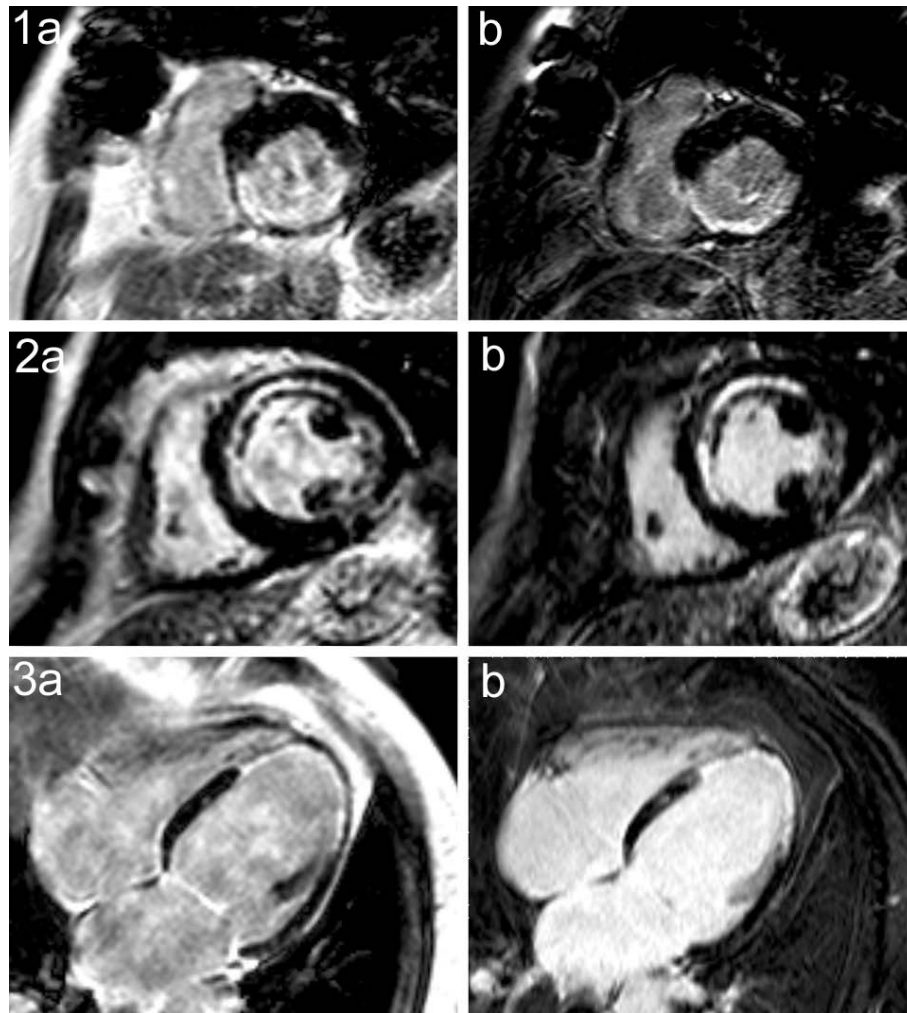
A group of 18 patients was examined about 15 minutes post-Gd when the decrease in relaxation rate is slow. The observed change in relaxation rates  $\Delta R_1$  for healthy myocardium and fibrotic myocardium is shown in Fig. 8. As base line reference  $R_1 = 1.2 \text{ s}^{-1}$  is taken. Linear regression estimated a slope between fibrotic and healthy myocardium of  $r = 2.5$  ( $R^2 = 0.93$ ).

As an additional validation the  $T_1$  maps were used as input for synthetic LGE images. Three examples are shown in Fig. 9 of three different patients. The inversion delay was set to a value that turned the healthy myocardium black (1: 234 ms, 2: 272 ms, 3: 267 ms). Next to the synthetic images (a) the corresponding actual IR-TFE measurements are shown (b). The inversion delay of this sequence was set to the predicted value of the synthetic images plus 20 ms to compensate for the time delay between the two scans (about 1 minute in all cases). The first example (1a) corresponds to slice 13, 16 minutes post-Gd as displayed in Fig. 5. Visual assessment shows similar pathologic findings in both image sets. An overall difference in contrast between the synthetic image and the conventional image can be seen due to the lack of a SPIR fat-suppression pulse in the quantification scan.

In order to compare the imaging methods two regions of interest were placed in all images, one in healthy and one in fibrotic myocardium. The Contrast to Noise Ratio (CNR) was defined as the difference in signal intensity of the two ROI's divided by the standard



**Figure 8** The change in relaxation rate  $\Delta R_1$  after Gadolinium compared to the base line reference  $R_1 = 1.2 \text{ s}^{-1}$ , at about 15 post-Gd. The indicated slope between healthy myocardium and fibrotic myocardium is  $r = 2.5$ .



**Figure 9 Comparison of synthesized LGE images with actual LGE images.** Synthesized inversion recovery images (a) compared with actual inversion recovery images (b) with the same inversion delay plus 20 ms of three different patients. The first patient is the same as in Figs. 5-7 (slice 13). The actual IR-TFE images show pathologies in a similar way but have higher resolution and more slices than the synthesized IR images. The inversion delay was optimal in all three cases based on the prediction of the synthetic images.

deviation in the ROI over the healthy (black) myocardium. Both methods turn out to have equal CNR ( $R^2 = 0.90$ ). A significant difference is, however, that the IR-TFE acquires more slices (22 - 17 compared to 18 - 10 of the PSIR) and a higher resolution (acquisition voxel size  $1.5 \times 1.6$  mm compared to  $1.5 \times 2.3$  mm of the PSIR) in the same scan time.

### Discussion

The validation of the absolute  $T_1$  relaxation time in phantoms, as depicted in Figs. 2 and 3, shows that our method is consistent over a large range of  $T_1$  values, flip angles and inversion delay times. As can be seen in Fig. 2 the optimal flip angle of the method is around 15-20 degrees where the signal to noise ratio is highest and the deviation from the expected value is low. The range

of inversion delays that can be chosen is large. The fitting algorithm consistently removes the saturation and acquisition effects. The observation that short  $T_1$  values in the order of 200 ms are consistently measured even with an inversion delay of up to 600 ms implies that the assumption of a perfect inversion pulse is valid. An imperfect inversion would lead to an overestimation of  $T_1$ . Possibly this issue has a larger influence at higher field strengths.

Typical  $T_1$  values for an LGE measurement are in the range 200 - 500 ms. Based on Fig 3 the inversion delay of the method can therefore be chosen anywhere in the range 300 - 600 ms. An inversion delay of 300 ms was selected for the *in-vivo* experiments mainly because it is close to the commonly used inversion delay. With these settings the proposed method correctly estimates  $T_1$

values even up to 800 ms although the kernel time is only 2 s. Although it was not the focus of this study it is likely that the method would work for pre-GD myocardial  $T_1$  values as well. In that case a more natural choice for the inversion delay would be higher, e.g. 600 ms.

In clinical practice other parameters are important, such as the variability of the heart-rate during breath-hold, which might decrease the accuracy of the  $T_1$  map. The Monte-Carlo simulation displayed in Fig. 4 shows that small changes in heart rate have less influence on the typical  $T_1$  values than the noise level of the measurement. Furthermore, the resulting error shifts all tissue of interest in a similar fashion and leaves the differences in  $T_1$  between the healthy and fibrotic myocardium virtually unaffected.

Care has to be taken in the interpretation of the absolute  $T_1$  relaxation time. A tissue voxel comprises of many  $T_1$  components rather than the mono-exponential decay that is assumed in the method. Furthermore, at the selected echo time the short-lived  $T_1$  components might be underestimated and the frequency difference between water and fat might lead to a spatial shift of the intensity in the images. Our 2-point method is designed to rapidly estimate the predominant component of  $T_1$  relaxation and for the given scanner parameters this is achieved.

A potential disadvantage of the method is the long breath-hold time (24 s). This results in 12-18 slices of 5 mm depending on the heart rate. Should this be too long the acquisition time may be decreased by reducing the number of slices. The reduced heart volume coverage may be compensated by increasing the slice thickness.

An example of the application of the method is given in Figs. 5, 6, 7 where a patient was monitored every 2 minutes post-Gd. A clear evolution of  $R_1$  is observed over time in the heart and the liver. The change of the relaxation rate  $\Delta R_1$  is taken here, rather than  $T_1$ , since  $\Delta R_1$  is proportional to the absolute amount of contrast medium present in the tissue and should therefore also represent the severity of fibrosis on a microscopic level. As known from practice the  $\Delta R_1$  rapidly decreases in the first 5-10 minutes to remain relatively flat in the following 10-30 minutes. The late enhancement contrast already appears after a few minutes. For our patient group the amount of contrast media was about 2.5 times higher in the fibrotic areas compared to the healthy areas (Fig. 8) at about 15 minutes post-Gd. Note that fat is unaffected by the contrast medium and hence can serve as a reference signal intensity for relative measurements of signal intensity during a contrast bolus for perfusion.

The approach of synthetic MRI is used for a direct comparison of the  $T_1$  quantification maps and conventional imaging resulting in very similar images as shown

in Fig. 9. Pathology shows up similarly and the method has a good CNR. Interestingly this approach also means that the quantification method may provide both the  $T_1$  maps and the relevant clinical images in one single scan. The ability to synthetically vary  $T_{inv}$  after the actual acquisition may optimize the image quality separately for both ventricles [26]. Moreover the method may serve as a test scan to optimize the  $T_{inv}$  for subsequent IR-TFE sequences.

## Conclusions

We present a method to quantify cardiac  $T_1$  relaxation in a large volume within a single breath-hold, based on a 3D Phase Sensitive Inversion Recovery sequence. The fitting algorithm takes acquisition and saturation effects into account and is robust against variation of scan parameters and heart rate. The method is independent of RF coil sensitivity issues such that high-SNR phased array coils can be employed. The absolute relaxation rate  $R_1$  is monitored over time and over a group of patients. The  $T_1$  maps can be used for 3D segmentation and synthesis of conventional LGE images with a free choice of inversion delay.

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## Authors' contributions

JBW developed and verified the theoretical model, JK organized and scanned the patient group and JE was responsible for recruiting, investigating and reporting on the patients. All three reviewed the manuscript.

## Competing interests

The main author (JBW) is partly employed by SyntheticMR AB. This software is used additionally for verification of the method.

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