Improved Quantitative Myocardial T\textsubscript{2} Mapping: Impact of the Fitting Model

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**Purpose:** To develop an improved T\textsubscript{2} prepared (T\textsubscript{2}prep) balanced steady-state free-precession (bSSFP) sequence and signal relaxation curve fitting method for myocardial T\textsubscript{2} mapping.

**Methods:** Myocardial T\textsubscript{2} mapping is commonly performed by acquisition of multiple T\textsubscript{2}prep bSSFP images and estimating the voxel-wise T\textsubscript{2} values using a two-parameter fit for relaxation. However, a two-parameter fit model does not take into account the effect of imaging pulses in a bSSFP sequence or other imperfections in T\textsubscript{2}prep RF pulses, which may decrease the robustness of T\textsubscript{2} mapping. Therefore, we propose a novel T\textsubscript{2} mapping sequence that incorporates an additional image acquired with saturation preparation, simulating a very long T\textsubscript{2}prep echo time. This enables the robust estimation of T\textsubscript{2} maps using a 3-parameter fit model, which captures the effect of imaging pulses and other imperfections. Phantom imaging is performed to compare the T\textsubscript{2} maps generated using the proposed 3-parameter model with the conventional two-parameter model, as well as a spin echo reference. In vivo imaging is performed on eight healthy subjects to compare the different fitting models.

**Results:** Phantom and in vivo data show that the T\textsubscript{2} values generated by the proposed 3-parameter model fitting do not change with different choices of the T\textsubscript{2}prep echo times, and are not statistically different than the reference values for the phantom (\(P = 0.10\) with three T\textsubscript{2}prep echoes). The two-parameter model exhibits dependence on the choice of T\textsubscript{2}prep echo times and are significantly different than the reference values (\(P = 0.01\) with three T\textsubscript{2}prep echoes).

**Conclusion:** The proposed imaging sequence in combination with a three-parameter model allows accurate measurement of myocardial T\textsubscript{2} values, which is independent of number and duration of T\textsubscript{2}prep echo times. **Magn Reson Med** 000:000–000, 2014. © 2014 Wiley Periodicals, Inc.

**Key words:** quantitative myocardial tissue characterization; myocardial T\textsubscript{2} mapping; three-parameter fit; myocardial inflammation

**INTRODUCTION**

T\textsubscript{2}-weighted images are commonly used in cardiac MR (CMR) to assess myocardial inflammation and edema in various cardiomyopathies. They have been shown to distinguish acute and chronic myocardial infarction (1), to identify severe transient myocardial ischemia (2), and to predict revascularization needs (3). T\textsubscript{2}-weighted imaging has also been used in patients with myocarditis (4,5), allograft rejection (6), and Takotsubo cardiomyopathy (7), where T\textsubscript{2} values are elevated. The T\textsubscript{2}-weighted imaging sequences used in these studies rely on turbo spin echo readouts with black-blood preparation (8). However, the T\textsubscript{2}-weighted imaging sequences suffer from certain limitations (9–11), including qualitative interpretation that is affected by regional differences; myocardial signal variation due to phased-array coil arrays; and difficulty differentiating edema from stagnant subendocardial blood.

Quantification of myocardial T\textsubscript{2} values (12,13) has been proposed as an alternative to T\textsubscript{2}-weighted imaging to reduce the variation in assessment. The earlier T\textsubscript{2} quantification sequences were based on spin echo/fast spin echo acquisitions (12–15). More recently, T\textsubscript{2} mapping techniques (11,16–20) have been proposed, where several images are acquired with different T\textsubscript{2}-weightings, and used to generate a quantitative pixel-wise T\textsubscript{2} map based on a spin–spin relaxation model compatible with the acquisition. T\textsubscript{2}-prepared (21) balanced steady-state free precession (bSSFP) techniques have been used for efficient T\textsubscript{2} mapping (22). In these techniques, several different T\textsubscript{2} prep preparation (T\textsubscript{2}prep) echo times are used to generate the multiple T\textsubscript{2}-weighted images (11,16–20). In one such approach, three electrocardiogram (ECG)-triggered single-shot bSSFP images are acquired with three different T\textsubscript{2}prep times (0 ms, 24 ms, 55 ms) with two heart-beat rest periods for signal recovery between each image, using a breath-hold acquisition (11,18). These images are subsequently registered and then fit to a 2-parameter fit model (consisting of the longitudinal magnetization without T\textsubscript{2}prep and the T\textsubscript{2} time) to generate the myocardial T\textsubscript{2} maps.

Despite the potential of myocardial T\textsubscript{2} mapping for quantitative assessment of myocardial inflammation and edema (18,19,23–26), it has still not replaced T\textsubscript{2}-weighted techniques in clinical CMR protocols. In terms of the sequence, single-shot bSSFP acquisitions following different T\textsubscript{2}prep echo times have replaced the spin echo approach. However, there is a lack of data about the robustness of T\textsubscript{2} estimation with respect to the choice and number of T\textsubscript{2}prep echo times when using the conventional sequences and the curve fitting model.

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In terms of the curve-fitting model, the two-parameter fit has been used extensively in the literature, both with spin echo acquisitions (12,14,27) or bSSFP acquisitions with various profile ordering schemes (16,20,22). However, the 2-parameter model ignores the changes in the $T_1/T_2$ contrast due to the imaging pulses until the acquisition of the center of $k$-space when using a bSSFP sequence, with several start-up pulses and especially with linear profile ordering. The shortcomings of the two-parameter model have been noted previously (17,28). In (17), an empirical offset parameter was included to account for the $T_1$ relaxation during the gradient echo sequence. This value was chosen based on Bloch simulations and was fixed for a given set of sequence parameters and physiology characteristics. In (28), a third parameter was empirically included to characterize the deviations from the two-parameter model in numerical simulations and phantom experiments, although no analytical insight was given regarding the necessity of such a term.

In this work, we propose a sequence and a signal recovery curve fitting model for improved myocardial $T_2$ mapping. We propose a three-parameter curve fitting model, where the third parameter captures the perturbations in the magnetization curve due to the imaging pulses played between the $T_2$ prep and the acquisition of the central $k$-space line. Our proposed sequence acquires multiple single-shot images with different $T_2$ prep echo times, followed by rest periods for magnetization recovery, as well as one saturation-prepared image. The latter captures the effect of imaging pulses on the magnetization curve, and thus improves the estimation of the third parameter. Additionally, to enable efficient free-breathing acquisitions in vivo, we propose a new NAV-gating scheme that applies $T_2$ prep conditionally based on the position of the NAV signal. This eliminates the necessity for rest periods if the NAV signal is outside of the gating window. Phantom experiments and in vivo imaging are performed to evaluate the proposed sequence and the recovery curve fitting model.

METHODS

The two-parameter curve fitting model typically used in myocardial $T_2$ mapping is given by:

$$M_{2\text{-parameter}}(t) = Ae^{-t/T_1}, \quad [1]$$

where $t$ is the $T_2$ prep echo time. In this work, we propose to use a 3-parameter model to capture the effect of imaging pulses on the magnetization

$$M_{3\text{-parameter}}(t) = Ae^{-t/T_2} + B. \quad [2]$$

The proposed sequence aims to improve the efficiency and accuracy of $T_2$ mapping, while addressing several aspects of this estimation procedure.

Proposed Sequence

Figure 1a shows the schematic of the proposed sequence. Multiple single-shot images of the heart are acquired using ECG-triggering, following $T_2$ prep (21) of different echo lengths, $TE_{T2P}$. Between each image, a 6 second rest period (with no RF pulses) is applied to allow for full re-growth of the myocardial signal. To improve the estimation of the third parameter ($B$), the sequence additionally acquires an image, $I_{SAT}$, directly after a saturation pulse to simulate the effect of a very long $T_2$ prep echo time (i.e., $T_2$ prep $= \infty$).

The $T_2$ prep itself consists of 90° tip-down pulse, followed by four 180° pulses and ends with 90° tip-up pulse. Both the opening and closing 90° pulses are non-selective hard pulses with a bandwidth of 2.3 kHz, and duration of 0.44 ms. These noncomposite short pulses were chosen to minimize any $T_2^*$ effect that might occur during the pulse. The refocus pulses are weighted in a MLEV opposing phase pairs scheme to compensate for RF pulse shape imperfection (29) and composite refocusing pulses (90°, 180°, 90°, 180°) are used to provide second order corrections to variations in $B_1$. The duration of each refocus pulse is 1.75 ms. For $I_{SAT}$, a composite saturation pulse of bandwidth $= 1$ kHz, and a total duration of 10 ms is used.

A common issue with $T_2$ prep sequences is the effect of $B_0$ and $B_1$ variations of the excitation and refocusing pulses of the $T_2$ prep sequence. In the proposed method, this will change the A parameter in Eq. [2] for all the images acquired with a nonzero $TE_{T2P}$. However, if $TE_{T2P} = 0$ is acquired with no contrast preparation as in (11), the A parameter for this term will not be affected by these inhomogeneity effects, leading to an inconsistency with the other $TE_{T2P}$ values. To compensate for this effect, we add a 90°, followed immediately by a −90°, followed by a crusher gradient, for the acquisition of a $TE_{T2P} = 0$, similar to the one proposed in (22). We hypothesize that this compensates for $B_0$ and $B_1$ variations, and removes the bias from the estimation of the $T_2$ parameter that would have been caused by RF flip angle imperfections.

The flowchart for the proposed navigator-gated acquisition scheme is depicted in Figure 1b. The NAV is placed immediately before the $T_2$ prep. For the acquisition of the $k$th image, $I_k$, if the NAV signal is outside the gating window, no $T_2$ prep or imaging pulses are applied, leaving the magnetization undisturbed, and the acquisition of $I_k$ is repeated in the next R-R interval. If the NAV signal is within the gating window, the image with the desired $T_2$ prep time is acquired, followed by a 6 second rest period for magnetization recovery. Figure 1c shows an example of the rejection-reacquisition scheme for a $T_2$-prepared image. Figure 1d also depicts the acquisition of a saturation-prepared (SAT) image, which immediately follows the $T_2$-prepared image without any rest periods, and where the NAV is placed before the saturation pulse.

Three-Parameter Model for $T_2$ Relaxation

We sought to characterize the effect of the bSSFP imaging pulses that are played until the acquisition of central $k$-space, on the magnetization measured after $T_2$ preparation. When a $T_2$ prep scheme (21) with a $T_2$ echo time of $TE_{T2P}$ is used, the longitudinal magnetization is given by:
\[ M_{\text{start}} = M_0 e^{-\frac{TE_{\text{prep}}}{T_2}}. \]  

where \( M_0 \) is the signal at full-recovery. When using a bSSFP readout with \( n \) RF pulses, the signal is given by

\[ M(n) = \sin \left( \frac{\alpha}{2} \right) M_{\text{start}} - M_{SS} \lambda_1^n + M_{SS}. \]  

where \( \alpha \) is the flip angle, and where the steady state magnetization, \( M_{SS} \) is given by

\[ M_{SS} = M_0 \frac{\sqrt{E_2(1 - E_1)\sin(\alpha)}}{1 - (E_1 - E_2)\cos(\alpha) - E_1 E_2}. \]  

with \( E_{1,2} = e^{-\frac{TR}{T_1}} \) and \( \lambda_1 = E_2 \sin^2(\alpha/2) + E_1 \cos^2(\alpha/2) \). This can be re-written as

\[ M(n) = \sin \left( \frac{\alpha}{2} \right) \lambda_1^n M_{\text{start}} + \left[ 1 - \lambda_1^n \right] M_{SS}. \]

\[ M_{SS} = (M_0 \sin(\alpha/2) \lambda_1^n) e^{-\frac{TE_{\text{prep}}}{T_2}} + \left[ 1 - \lambda_1^n \right] M_{SS}. \]  

Thus, for \( T_2 \)-prepared bSSFP acquisitions, in which several imaging pulses are used before the acquisition of 

the center of k-space, the \( T_2 \) relaxation between the different images can be characterized as:

\[ M_{\text{3-parameter}}(TE_{\text{prep}}) = Ae^{-\frac{TE_{\text{prep}}}{T_2}} + B, \]  

where the parameters, \( A \) and \( B \) do not depend on the \( T_2\text{prep} \) time, \( TE_{\text{prep}} \). However, they are functions of the sequence parameters (flip angle, number of pulses, repetition time, etc). Furthermore, based on Eq. [6], we note that \( B \) captures the effect of the imaging pulses, when \( M_{\text{start}} = 0 \).

### T2 Map Reconstruction

\( T_2 \) maps are generated by voxel-wise least-squares curve-fitting to the magnitude signal intensity. Both the two-parameter model in Eq. [1] and the three-parameter model in Eq. [2] are used. The following curve-fitting methods are performed for the experiments:

1. The two-parameter model with various \( T_2\text{prep} \) echo times. This method does not include the SAT image, because the two-parameter signal model decays to 0 for large \( T_2\text{prep} \) echo times.
2. The three-parameter model with various T2prep echo times and with the saturation-prepared image. The SAT image is equivalently characterized as a very long T2prep echo time (i.e., T2prep = \infty).

3. The 3-parameter model with various T2prep echo times and without the SAT image.

Numerical Simulations: B1 Field Inhomogeneity

Numerical simulations were conducted to study the effect of B0 and B1 variations on the estimated T2 values, and to characterize the effect of using the proposed 90°, -90° and crusher gradient preparation during the acquisition of a TE_{T2P} = 0 on these T2 estimations. Bloch equation was simulated to consider the effect of spin rotation around B_0 instead of B_1 during the 90°, -90°, and 180° pulses of the T2prep, with

\[ B_{\text{eff}} = B_1 \hat{i} + \left( B_0 - \frac{\omega}{\gamma} \right) \hat{k}, \]

where B_0 is the strength of the magnetic field in the z-direction, \( \gamma \) is the gyromagnetic ratio, and B_1 and \( \omega \) are the strength and frequency of the applied RF pulse respectively.

Nominal myocardium T1 and T2 values (i.e., 1200 ms and 50 ms, respectively at 1.5 Tesla) were assumed for the simulations. The sequence was simulated to acquire T2prep echo times of 0, 25, and 50 ms, as well as the saturation-prepared image. Then, both the 2-parameter and 3-parameter fits were used to estimate the T2 values, and the absolute error from the true T2 value was recorded for different variations of B_0 and B_1. The simulation was repeated with and without the proposed compensation for TE_{T2P} = 0.

Phantom Imaging

All imaging was performed on a 1.5 Tesla (T) Philips Achieva (Philips Healthcare, Best, The Netherlands) system using a 32-channel cardiac coil array. Phantom imaging was performed using NiCl_2 doped agarose vials, whose T2 and T1 values spanned the ranges of values found in the blood and myocardium. A single-shot ECG-triggered bSSFP sequence with the following parameters was used for the proposed sequence: 2D single-slice, field of view (FOV) = 240 \times 240 \text{ mm}^2, in-plane resolution = 2.5 \times 2.5 \text{ mm}^2, slice thickness = 8 \text{ mm}, repetition time/echo time (TR/TE) = 2.7 \text{ ms}/1.35 \text{ ms}, flip angle = 85°, 10 linear ramp-up pulses, SENSE rate = 2, acquisition window = 138 ms, number of phase encoding lines = 51, linear k-space ordering. A total of 27 different T2prep echo times were used, including TE_{T2P} = 0 and TE_{T2P} ranging from 25 ms to 150 ms in steps of 5 ms. Additionally one image was acquired after saturation preparation for the three-parameter fit.

A Carr-Purcell-Meiboom-Gill (CPMG) spin-echo sequence with an echo train length of 32 with TE 10 ms was performed as reference. The scan parameters were: FOV = 240 \times 240 \text{ mm}^2, in-plane resolution = 1.25 \times 1.25 \text{ mm}^2, slice thickness = 4 \text{ mm}, TR = 6000 \text{ ms}, flip angle = 90°. Number of averages = 4, reference T2 times were obtained from a 2-parameter model fit to the spin echo signal.

Three-Parameter versus Two-Parameter Fit: Effect of T2prep Echo Times

We hypothesized that the estimated T2 values would be independent of the T2prep times used to sample the images if the true magnetization model and the curve-fitting model matched. On the other hand, the estimated T2 values would change based on the T2prep times sampled if there was mismatch between the true magnetization model and the curve-fitting model. To test this hypothesis, two-parameter and three-parameter models were used to generate T2 maps based on different subsets of images corresponding to different T2prep echo times. The following subsets were used:

- a. TE_{T2P} = 0 and n TE_{T2P} values starting from 25 ms in steps of 5 ms (n from 2 to 26).
- b. TE_{T2P} = 0 and n TE_{T2P} values starting from 25 ms in steps of 10 ms (n from 2 to 13).
- c. TE_{T2P} = 0 and n TE_{T2P} values starting from 25 ms in steps of 15 ms (n from 2 to 9).
- d. TE_{T2P} = 0 and n TE_{T2P} values starting from 25 ms in steps of 20 ms (n from 2 to 7).
- e. TE_{T2P} = 0 and n TE_{T2P} values starting from 25 ms in steps of 25 ms (n from 2 to 6).

As described previously, the additional SAT image is used with the three-parameter model, and not used with the two-parameter model. To quantify the effect of using the SAT image in the three-parameter fit on accuracy and precision, these experiments were also repeated using the three-parameter model but excluding the SAT image from the curve-fitting process.

Additionally, T2 map estimation was performed using three T2prep echoes (0, 25, 50 ms), similar to the ones used in the literature (11,17,18) using a two-parameter fit. Three-parameter fit was performed using these three echoes and the proposed SAT image. Three-parameter fit was also performed using a 4th echo at 90 ms instead of the SAT image. These acquisitions are referred to as the short acquisition with two-parameter, three-parameter fit with SAT, and three-parameter without SAT, respectively.

Effect of the B1 Inhomogeneities

To quantify the effect of using the 90°, -90° & crusher gradient preparation during the acquisition of a TE_{T2P} = 0 to compensate for any RF pulse imperfection, imaging was performed with and without (i.e., no pulses applied) this correction. The two-parameter and three-parameter fits were performed for all echoes for both acquisitions. An additional SAT image was used for the 3-parameter fit as previously described.

Length of the Rest Cycles

Rest cycles are used after the acquisition of each single-shot image to allow for magnetization recovery. Imaging was performed to study the effect of the length of these rest cycles, using rest cycle lengths varying from 0 to 9 s.
Accurate Myocardial T₂ Mapping

T₂ Map Analysis

A region-of-interest (ROI) analysis was performed, where the mean value and standard deviation was recorded for each vial for each calculated T₂ map. Accuracy was assessed as the difference between the mean of the vial for the spin echo reference T₂ map and the mean of the vial for the given T₂ map. Precision was assessed as the standard deviation of the vial for the given T₂ map. The null hypotheses that there was no difference in the mean value for a vial in the spin echo reference and in a given T₂ map was tested using a paired t-test across all vials. A P value of <0.05 was considered to be significant.

In Vivo Imaging

This portion of the study was approved by the institutional review board and written informed consent was acquired before each examination. In a prospective study, eight healthy adult subjects (30.3 ± 17.5 years, range: 22–73 years, 4 men) without contraindications to MRI were recruited. For each subject, localizer scouts were acquired to define the mid-ventricular short-axis slice. A two-dimensional spiral NAV echo was positioned on the right hemi-diaphragm, and was used for gating with a 5 mm gating window. A free-breathing single-shot ECG-triggered bSSFP sequence with the following parameters was used for the acquisition of the mid-ventricular short-axis slice: 2D single-slice, FOV = 320 × 320 mm², in-plane resolution = 2.5 × 2.5 mm², slice thickness = 8 mm, TR/TE = 2.7 ms/1.35 ms, flip angle = 85°, 10 linear ramp-up pulses, SENSE rate = 2, acquisition window = 181 ms, number of phase encoding lines = 67, linear k-space ordering. All acquisitions were performed with 27 images corresponding to different T₂prep echo times, including TET₂P = 0 and TET₂P ranging from 25 ms to 150 ms in steps of 5 ms. An additional SAT image was also acquired for the 3-parameter fit. T₂ maps were also generated for the short acquisition configurations. The nominal scan time for these scans, acquiring all 27 T₂prep echoes, was 3:10 min at 60 heartbeats per min, assuming 100% NAV gating efficiency.

T₂ Map Analysis

The acquired images were registered retrospectively using an advanced nonrigid image registration algorithm (32) to compensate for residual in-slice motion. This algorithm simultaneously estimates a nonrigid motion field and intensity variations, and uses an additional regularization term to constrain the deformation field using automatic feature tracking. Voxel-wise curve-fitting was performed, subsequent to registration, to generate T₂ maps for the three-parameter and the two-parameter models. T₂ maps were generated for different subsets of images corresponding to different T₂prep echo times, as described for phantom imaging. Epi- and endocardial contours were drawn manually by an experienced blinded reader for each T₂ map. The average T₂ value and the standard deviation within the septum were recorded.

Finally, a segment-based analysis was performed for the proposed three-parameter model with the SAT images. Variations in T₂ and B/A across different segments were studied to see if the regional variations were due to tissue characteristics or due to sequence parameters, as described by Eq. [6]. Six segments were used in the mid-ventricular LV slice, in accordance with the AHA 16-segment model (33). Segment-based T₂ and B/A values were recorded for each subject. These were then averaged over all subjects for each segment. The B/A value was also compared with the value predicted by Eq. [6] for the given sequence parameters.

RESULTS

Numerical Simulations

Figure 2 shows the effect of B₀ and B₁ variations on T₂ estimation. Figure 2a shows the normalized longitudinal magnetization measured directly after the T₂prep pulse. Figures 2b–d show the errors in T₂ estimation using two-parameter fit, and three-parameter fit, with and without the proposed compensation of 90°, −90° pulses for TET₂P = 0. The green area in Figure 2b shows valid T₂ estimations (within ±5 ms) over a B₀ range of ±200 Hz and a B₁ range of 20%. Using the three-parameter fit in Figure 2d reduced the B₀ range to around ±150 Hz but increased the B₁ range to nearly 30%. However, when the proposed 90°, −90° was used for TET₂P = 0, the B₀ range to increased to almost 250 Hz with the same B₁ range (Figure 2e). This was not the case with the two-parameter fit in Figure 2c where a bias of 10–30 ms was observed in the estimated T₂ values for almost the whole range of B₀–B₁ variations.

Phantom Imaging

Three-Parameter versus Two-Parameter Fit

Figure 3 shows the accuracy and precision of the three different fitting approaches (two-parameter, three-parameter without SAT image and the proposed three-parameter with SAT image) on various subsets of images corresponding to different T₂prep echo times for a vial with a T₂ value of 47 ms. The red, green, blue, purple, and black points correspond to TET₂P = 0 and n TET₂P values starting from 25 ms in steps of 5, 10, 15, 20, and 25 ms, respectively, and the value of n is depicted on the horizontal axis. The T₂ value estimated with the 2-parameter model increased with the number of T₂prep echoes. For example, a two-parameter fit on 9 T₂prep echoes resulted in an estimated T₂ value of 64 ms, as opposed to an estimate of 55 ms for 5 T₂prep echoes, when a 10 ms TET₂P spacing was used. The echo spacing also affected the estimated T₂ value for the 2-parameter model. For example, using 7 T₂prep echo times, a 5 ms TET₂P spacing led to a 55 ms T₂ estimate, whereas a 25 ms TET₂P spacing resulted in the estimation of 63 ms as the T₂ value. These exemplify the mismatch between the acquisition and the two-parameter model. The three-parameter fit without SAT image converged to the T₂
value after 7 T2prep echoes. However, if the number of T2prep echoes was not sufficient, it overestimated the T2 value, with a high level of noise as apparent in the precision measurements. The T2 value estimated using the three-parameter fit with the SAT image remained almost constant (variation: 2 ms) for different subsets of T2prep echo times. Figure 4 shows examples of the fit for the short acquisition and for 27 T2prep echoes, for the same vial, where the signal in the ROI is averaged before fitting. The overestimation of the T2 value using three T2prep echoes and the two-parameter fit were visualized in the under-estimation of the nonzero signal value corresponding to the long T2prep echo time (“T2prep = ∞”). When using 27 echoes, the three-parameter fit without SAT image matched the behavior of the proposed three-parameter fit with SAT image, while the two-parameter fit still overestimated the T2 values.

Figure 5 depicts the correlation of the different T2 curve fitting methods using the short acquisition or all 27 T2prep echoes, with respect to the spin echo sequence. The proposed three-parameter fit with SAT image, using the short acquisition or all 27 T2prep echoes, produced T2 values that were not significantly different than the reference values generated using a spin echo acquisition (P = 0.104 and 0.3, respectively). The three-parameter fit without SAT image showed no significant differences for both the short acquisition and 27 T2prep echoes (P = 0.073 and 0.126, respectively). The conventional 2-parameter fit significantly overestimated the T2 values for both 3 and 27 T2prep echoes (P = 0.013 and 0.005, respectively).

**Effect of the B1 Inhomogeneities**

The T2 values using the proposed 3-parameter fit with SAT image were not significantly different than the spin echo values, as described above, when using the proposed RF compensation (P = 0.3). However, the difference was significant without the compensation (P < 0.001). The two-parameter fit led to significant differences in T2 values, both with and without the compensation (P = 0.005 and 0.010, respectively).

**Length of the Rest Cycles**

Figure 6 shows the effect of the length of rest cycles. The error in the estimated T2 was the highest for vials with long T1 values due to insufficient magnetization recovery. This error gradually decreased with increasing rest cycles. For the vials with T1 and T2 ranges near the myocardium and for rest cycles ≥ 4 s, the error was within 2 ms and 1 ms when using the short acquisition and 27 samples, respectively.
In Vivo Imaging

The myocardial T$_2$ mapping sequence was successfully completed in all subjects without complications. The average scan time to acquire all 27 echoes was $3:30 \pm 0:10$ min (range: $3:17$ to $3:47$ min). The difference between the nominal scan time and the actual average scan time is due to the differences in breathing patterns and heart rates of the subjects. Figure 7 shows example T$_2$ maps from a healthy subject, generated using the three different fitting approaches (two-parameter, three-parameter without saturation-prepared (SAT) image and the proposed three-parameter with SAT image) on various subsets of images corresponding to different T$_{2\text{prep}}$ echo times for a vial with a T$_2$ value of 47 ms. The T$_2$ value estimated with the two-parameter model (a) shows dependence on the choice and number of T$_{2\text{prep}}$ echo times. The three-parameter fit without SAT image (b) showed large deviations in accuracy and precision for a small number of T$_{2\text{prep}}$ echoes, but converged to the T$_2$ value with a large number of T$_{2\text{prep}}$ echoes. The T$_2$ value estimated using the proposed three-parameter fit with the SAT image (c) remained almost constant (variation: 2 ms) for different subsets of T$_{2\text{prep}}$ echo times. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 3. Accuracy and precision of the three different fitting approaches (2-parameter, 3-parameter without saturation-prepared (SAT) image and the proposed 3-parameter with SAT image) on various subsets of images corresponding to different T$_{2\text{prep}}$ echo times for a vial with a T$_2$ value of 47 ms. The T$_2$ value estimated with the two-parameter model (a) shows dependence on the choice and number of T$_{2\text{prep}}$ echo times. The three-parameter fit without SAT image (b) showed large deviations in accuracy and precision for a small number of T$_{2\text{prep}}$ echoes, but converged to the T$_2$ value with a large number of T$_{2\text{prep}}$ echoes. The T$_2$ value estimated using the proposed three-parameter fit with the SAT image (c) remained almost constant (variation: 2 ms) for different subsets of T$_{2\text{prep}}$ echo times. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIG. 4. Example of the fit for the short acquisition and using 27 T$_{2\text{prep}}$ echoes, for the same vial in Figure 3, where the signal in the region of interest (ROI) is averaged before fitting. With the short acquisition, the two-parameter overestimates the T$_2$ value, as apparent in the under-estimation of the nonzero signal for “T$_{2\text{prep}}$ = $\infty$.” The proposed three-parameter fit with SAT image fits this signal value well for both 3 and 27 T$_{2\text{prep}}$ echoes. With 27 echoes, the three-parameter fit without SAT image matches the behavior of the proposed three-parameter fit with SAT image, while the two-parameter fit still overestimates the T$_2$ values. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
instead of three, which was consistent with phantom imaging. For the short acquisitions, the T2 map generated using the three-parameter fit without SAT image visibly showed more signal inhomogeneity compared with that of the proposed three-parameter fit with SAT. In the lower row, T2 values are estimated using long acquisitions (i.e., all 27 T2prep echoes). The conventional two-parameter fit significantly overestimates the T2 values for both three and 27 T2prep echoes (P = 0.013 and 0.005, respectively). The three-parameter fit without SAT image results in no significant difference for either the short acquisition echoes (P = 0.073) or with 27 T2prep echoes (P = 0.126). The proposed three-parameter fit with SAT image, using 3 or 27 T2prep echoes, produces T2 values that are not significantly different than the reference values (P = 0.104 and 0.3, respectively).

Figure 8 shows the estimated T2 values (averaged over an ROI in the septum) from the same subject in Figure 7 using the three fitting methods (two-parameter, three-parameter without SAT image, and the proposed three-parameter fit with SAT image) on various subsets of images corresponding to different T2prep echo times. Similar to phantom imaging, the T2 value estimated with the two-parameter fitting method increased with increasing number of T2prep echo times. The T2 value estimated using the three-parameter fit without SAT image showed a convergence trend with increased number of T2prep echo times. The T2 value estimated using the three-parameter fit without SAT image showed a convergence trend with increased number of T2prep echo times. The proposed three-parameter fitting with SAT image yielded T2 values which are independent of

FIG. 5. T₂ values from different T₂ curve fitting methods versus the reference T₂ values generated from the spin echo sequence for all vials of the phantom, as well as the identity line. In the upper row, T₂ values are estimated using short acquisitions (i.e., 3 (0, 25, 50 ms) samples for the two-parameter fit, four samples (0, 25, 50, 90 ms) for the three-parameter fit without SAT, and four samples (0, 25, 50, ∞ ms) for the three-parameter fit with SAT. In the lower row, T₂ values are estimated using long acquisitions (i.e., all 27 T₂prep echoes). The conventional two-parameter fit significantly overestimates the T₂ values for both three and 27 T₂prep echoes (P = 0.013 and 0.005, respectively). The three-parameter fit without SAT image results in no significant difference for either the short acquisition echoes (P = 0.073) or with 27 T₂prep echoes (P = 0.126). The proposed three-parameter fit with SAT image, using 3 or 27 T₂prep echoes, produces T₂ values that are not significantly different than the reference values (P = 0.104 and 0.3, respectively).

FIG. 6. Rest cycle’s effect on the estimated T₂ values. ROIs are placed in vials with different T₁ and T₂ values. The error is within 2 ms for both acquisitions when using rest cycles of length ≥ 4 s. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
number of T2prep echoes. The standard deviation of T2 values in the ROI decreased with higher number of echoes for all fitting methods.

Table 1 summarizes the ventricular septum T2 values for all of the healthy adult subjects using the three fitting methods, and the short acquisition or 27 T2prep echoes. The maximum variation (among all subjects) of the myocardial T2 value increases when going from 3 to 27 echoes using the two-parameter fit. For the short acquisition, the T2 map generated using the three-parameter fit without SAT image has 1.8-fold more variation in the septum compared with that generated using the proposed three-parameter fit with SAT image. When using all 27 T2prep echoes, the three-parameter fits with and without SAT image leads to similar quality in the myocardium.

![myocardial T2 values comparison](image1)

**FIG. 7.** Example T2 maps from a healthy adult subject (No. 3), generated using two-parameter fitting (left column), three-parameter fitting without SAT image (middle column) and the proposed three-parameter with SAT image (right column) with the short acquisition and using all 27 (top and bottom row respectively) T2prep echoes. The myocardial T2 value increases when going from 3 to 27 echoes using the two-parameter fit. For the short acquisition, the T2 map generated using the three-parameter fit without SAT image has 1.8-fold more variation in the septum compared with that generated using the proposed three-parameter fit with SAT image. When using all 27 T2prep echoes, the three-parameter fits with and without SAT image leads to similar quality in the myocardium.

![myocardial T2 values comparison](image2)

**FIG. 8.** Myocardial T2 values from the same subject in Figure 7 (averaged over an ROI in the septum) using two-parameter fit, three-parameter fit without SAT image and the proposed three-parameter fit with SAT image, on various subsets of image corresponding to different T2prep echo times. The two-parameter model (a) shows dependence on the choice and number of T2prep echo times. The three-parameter fit without SAT image (b) converges to the T2 value with a large number of T2prep echoes, but shows deviations otherwise. The proposed three-parameter fit with the SAT image (c) results in T2 values that are almost constant (variation: 3.6 ms) over different subsets of T2prep echo times.
Quantitative Myocardial $T_2$ Values in the Ventricular Septum Using Two-Parameter Fitting, Three-Parameter Fitting with and without SAT Image for the Short Acquisition and 27 $T_2$prep Echoes$^a$

<table>
<thead>
<tr>
<th>Subject</th>
<th>2-parameter Fit</th>
<th>3-parameter Fit, no SAT</th>
<th>3-parameter Fit, with SAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short Acq (ms)</td>
<td>27-echoes (ms)</td>
<td>Short Acq (ms)</td>
</tr>
<tr>
<td>1</td>
<td>68.2 ± 8.0</td>
<td>88.2 ± 10.3</td>
<td>56.2 ± 12.0</td>
</tr>
<tr>
<td>2</td>
<td>78.4 ± 14.3</td>
<td>87.3 ± 8.4</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>63.3 ± 11.3</td>
<td>77.5 ± 6.1</td>
<td>50.3 ± 8.8</td>
</tr>
<tr>
<td>4</td>
<td>56.3 ± 10.5</td>
<td>74.3 ± 15.8</td>
<td>36.6 ± 13.0</td>
</tr>
<tr>
<td>5</td>
<td>71.0 ± 9.4</td>
<td>75.6 ± 8.4</td>
<td>75.9 ± 22.4</td>
</tr>
<tr>
<td>6</td>
<td>71.0 ± 14.2</td>
<td>79.4 ± 9.7</td>
<td>N/A</td>
</tr>
<tr>
<td>7</td>
<td>67.7 ± 11.0</td>
<td>75.4 ± 14.1</td>
<td>68.3 ± 19.5</td>
</tr>
<tr>
<td>8</td>
<td>62.4 ± 10.6</td>
<td>73.5 ± 12.2</td>
<td>55.0 ± 17.1</td>
</tr>
<tr>
<td>average</td>
<td>67.3</td>
<td>78.9</td>
<td>57.1</td>
</tr>
</tbody>
</table>

$^a$The short acquisition consists of $T_2$prep echoes (0, 25, 50 ms) for the two-parameter fit; (0, 25, 50, 90 ms) three-parameter fit without SAT image; and (0, 25, 50, $\infty$ ms) for the three-parameter fit with SAT image.

Among all subjects, was 4.6–20.0 ms when the two-parameter fit is used with 27 $T_2$prep echoes instead of 3 $T_2$prep echoes. $T_2$ measurements could not be performed on two maps generated using the three-parameter fitting without SAT image and the short acquisition due to the high levels of inhomogeneity in the myocardium. Furthermore, for the $T_2$ maps from the short acquisitions where measurements could be performed, the precision of the three-parameter fit with the SAT image was significantly better than that of the three-parameter fit without the SAT image (8.5 ± 2.1 ms versus 15.5 ± 5.1 ms, $P=0.009$).

Table 2 depicts the results of the segment-based analysis for the proposed 3-parameter fit with 27 echoes. The range variation for the average $T_2$ values across the six segments is 4.2 ms (between 52.6 and 56.8 ms), showing less than 10% variation. The range of variation for the B/A values is 0.01, with a mean value of 0.14 or 0.15 across all segments. The B/A value predicted by Eq. [6] for these sequence parameters is 0.13 (with $T_1=1200$ ms and $T_2=55$ ms), which is consistent with the experimental findings.

**DISCUSSION**

In this study, we proposed a three-parameter model for $T_2$ relaxation to characterize $T_2$-prepared bSSFP acquisitions. For efficient estimation of these three parameters, we also proposed a novel sequence that incorporates saturation-prepared images in addition to $T_2$-prepared images, as well as an efficient navigator-gating scheme for free-breathing acquisitions. This new sequence and the three-parameter model improve the accuracy of myocardial $T_2$ mapping.

The three-parameter model for curve-fitting was found to be independent of the choice of $T_2$prep echo times, whereas the estimated $T_2$ values changed with $T_2$prep echo times using the two-parameter model. Because the two-parameter model does not take into account the disturbance in magnetization due to the startup and imaging pulses until the acquisition of central k-space, this leads to a model mismatch between the curve-fitting and the underlying acquisition, which makes the estimated $T_2$ value a function of the $T_2$prep echo times. This model mismatch is resolved using the three-parameter model, and the dependence of the estimated $T_2$ value on where the $T_2$ relaxation curve is sampled is eliminated.

Apart from its independence from the sequence parameters, the three-parameter model with the SAT image is accurate with respect to the spin echo sequence, after the proposed modifications to account for RF pulse imperfection. The inaccuracy of $T_2$ mapping procedure with the two-parameter curve-fitting with respect to the spin echo sequence, as well as its dependence on k-space profile ordering, has been noted previously (11). However, this discrepancy was not examined further in (11).

The reference $T_2$ maps with CPMG spin echo sequence were generated with a two-parameter fit. The issue of magnetization disturbance due to imaging pulses in single shot sequences is not present for this acquisition, thus a two-parameter fit is appropriate. The three-parameter fit for the spin echo acquisition (not shown) also yields the same values.

We chose to acquire 27 images with different $T_2$prep echo times in each scan for this study. This was done to study the effect of different choices of $T_2$prep times on the overall estimation procedure using the three-parameter and two-parameter models. This number of echoes is not required for attaining accuracy and precision for in vivo imaging using the proposed 3-parameter curve fitting with the additional SAT image. Furthermore, the precision gain going from 3 echoes to 27 echoes is at most 4.3 ms for the myocardium in this technique.

In (28), it was concluded that the three-parameter fit cannot be robustly used with four finite $T_2$prep echoes. However, our experience indicates that three $T_2$prep echoes of 0, 25, 50 ms, and an additional SAT image are sufficient to provide accurate and precise $T_2$ maps. Using 6-s rest cycles, this exam can be completed in 16 s at 60 bpm heart-rate, which is attainable with a breath-hold acquisition. The improvement in our sequence in terms of robustness with a small number of $T_2$prep echoes comes from the use of the SAT image instead of a large $T_2$prep echo time, which significantly improves the precision in vivo. Compared with the sampling of a large $T_2$prep echo time, such as 90 ms, the SAT image...
(equivalently T2prep echo time $\infty$) enables direct estimation of the B parameter in Eq. [2], and higher quality estimates of T2 values. Furthermore, in Appendix A, we analytically show that from an estimation theoretic perspective, sampling the SAT image is more beneficial in terms of precision of T2 maps in the presence of noise compared with sampling a large but finite T2prep echo time. Another benefit of using the SAT image is that it can be acquired without any preceding rest periods, whereas a 6-s rest period would be necessary to acquire a large T2prep echo time.

The segment-based analysis of the B/A parameter from the fitting procedure leads to values which are consistent with the theoretical predictions. The minor pixel-dependent differences may be due to the least squares fitting procedure, which approximates the Rician noise in the images as Gaussian noise with a nonzero mean (34), which would be reflected in the B parameter. Due to this good correspondence between theory as predicted in Eq. [6] and the experimental results, the utility of the B term is expected to extend to different phase encode schemes. Small regional variations of the T2 values were also observed.

For both the SAT image and for images acquired with large T2prep echo times, the underlying SNR may be too low to approximate the Rician noise as Gaussian noise, which is implicitly done in the least squares estimation process. This may cause a bias in the estimation procedure. However, this was not observed in our phantom experiments. Nonetheless, it might be beneficial to acquire multiple SAT images, because no rest cycles are required between them, and average them before fitting to further mitigate any bias.

Apart from the use of SAT images instead of large T2prep echo times, optimal selection of T2prep echo times to further improve robustness was not explored experimentally. In Appendix A, an estimation theoretic analysis to maximize the precision of the T2 maps shows that it would be beneficial to choose a tri-modal distribution of T2prep echo times, with the points concentrating at 0 ms, at an echo time near the T2 value of interest and at $\infty$, with the multiplicity changing based on the total number of echoes. However, in our experiments, we used a more standard distribution of T2prep echo times based on the existing literature. Further experiments are warranted to systematically optimize the T2prep echo time distribution, but this is not the focus of the current work.

A new navigator-gating scheme was proposed to improve the efficiency for free-breathing acquisitions. In the conventional scheme proposed in (35), the T2prep follows the NAV signal, however it is performed regardless of the position of the NAV signal, necessitating additional rest periods if the NAV signal is outside the gating window. In our proposed approach, the T2prep is conditionally applied based on the position of the NAV signal. Thus, if the NAV signal is outside the gating window, no preparation or imaging pulses are applied, and the magnetization remains undisturbed. This also eliminates the necessity for rest periods if the NAV signal is outside the gating window. Thus, the overall efficiency of the acquisition is improved.

Because the NAV signal is placed before the T2 preparation, there is a longer separation between the image

| Table 2: Segment-Based Analysis for the Proposed 3-Parameter Fit with 27 Echoes |
|----------------|------------------|------------------|
| Subj Seg B/A | T2 (ms) | B/A |
| 1 | 1 | 1.4 | 0.18 |
| 2 | 2 | 1.6 | 0.20 |
| 3 | 3 | 1.7 | 0.18 |
| 4 | 4 | 1.9 | 0.15 |
| 5 | 5 | 1.8 | 0.20 |
| 6 | 6 | 1.6 | 0.18 |

The results show that the range of variation for average T2 values across the six mid-ventricular myocardial segments is 4.2 ms. The range of variation for the B/A parameter is 0.01. The value predicted for B/A by Eq. [6] for the given sequence parameters is 0.13 (subject, seg = subject, seg = segment).
acquisition and the NAV signal. This may lead to residual motion in the images, necessitating image registration to mitigate residual motion artifacts. The efficacy of the particular image registration algorithm in $T_2$ mapping was not systematically studied in this study, and is beyond the scope and focus of this work.

A 6-s rest period was used to allow for a full magnetization recovery between subsequent $T_2$prep modules. This choice was based on a $5 \times T_1$ approximation, using reported myocardial $T_1$ values in the literature. While a 6-s rest period was used in this study to ensure sufficient recovery, phantom results indicated that 4 s may be sufficient, reducing the breath-hold duration for an acquisition with three $T_2$prep echoes and a SAT image. Although shorter rest periods are desirable, phantom results showed arbitrary, $T_1$-dependent biases in the estimated $T_2$ values when shorter durations were used.

This study has several limitations. Only a small number of healthy subjects were recruited. Further clinical evaluations on larger cohorts are warranted to quantify changes in $T_2$ relaxation times in different populations. No validation of the $T_2$ values has been performed in vivo, because a reference $T_2$ time cannot be assessed in the myocardium in a reasonable scan time. The in-patient reproducibility of the $T_2$ values was also not studied. We have only considered single-shot sequences with linear ordering. The effect of including the third parameter on accuracy may be less for centric ordering or multi-shot sequences. Only a single midventricular short-axis slice was imaged in this study. The low in-plane resolution used in this study may lead to partial imaging artifacts if more apical slices are acquired.

CONCLUSIONS

We propose a three-parameter model for $T_2$ relaxation accurately models myocardial $T_2$ mapping using $T_2$-prepared bSSFP acquisitions. This model exhibits no dependency on the choice of $T_2$prep echo times, whereas such dependence is observed if a conventional two-parameter model is used for curve-fitting. The proposed sequence incorporates SAT images in addition to $T_2$-prepared images, and the improved navigator-gating technique augments the efficiency of the myocardial $T_2$ mapping acquisition, allowing for accurate and precise $T_2$ maps.

ACKNOWLEDGMENTS

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APPENDIX A

We use the Cramér-Rao Bound (CRB) to provide a lower bound on the precision of an unbiased $T_2$ estimator, and subsequently minimize this bound numerically to find the optimal selection of $T_2$prep echo times, similar to the approaches in (36,37). For the model in Eq. [7] with least squares estimation of $T_2$, and for $K$ $T_2$prep echo times, $\{x_1, x_2, \ldots, x_K\}$, the Fisher information matrix is given by

\[
I = \begin{bmatrix}
\sum_{k=1}^{K} \left( \frac{x_k}{T_2^2} \right)^2 & \sum_{k=1}^{K} \frac{x_k}{\tau} & \sum_{k=1}^{K} \left( \frac{x_k}{\tau T_2^2} \right) \\
\sum_{k=1}^{K} \frac{x_k}{\tau} & \sum_{k=1}^{K} (1)^2 & \sum_{k=1}^{K} \left( \frac{x_k}{\tau T_2^2} \right) \\
\sum_{k=1}^{K} \left( \frac{x_k}{\tau T_2^2} \right) & \sum_{k=1}^{K} \left( \frac{x_k}{\tau T_2^2} \right) & \sum_{k=1}^{K} \left( \frac{x_k}{\tau T_2^2} \right)^2
\end{bmatrix}
\]  

[A1]

The CRB on the variance of the $T_2$ estimate is given by

\[
\text{var} \left( \hat{T}_2 \right) \geq J(A, T_2, \{x_k\}) = [I^{-1}]_{1,1}
\]

\[
= \frac{I_{11} I_{12} - I_{13}^2}{I_{11} (I_{22} I_{33} - I_{23}^2) - I_{12} (I_{13} I_{23} - I_{12} I_{33}) + I_{13} (I_{12} I_{33} - I_{13} I_{22})}
\]  

[A2]

where $I_{ij}$ denotes the $(i,j)$th entry of $I$. To find the selection of $T_2$prep echo times that minimizes the variance of the error, we propose to solve

\[
\{x_k^{\text{comp}}\} = \arg \min_{\{x_k\}} J(A, T_2, \{x_k\})
\]  

[A3]

for a given range of $T_2$ values of interest. We also note that $J(A, T_2, \{x_k\})$ scales with $1/A^2$, and thus $J(A, T_2, \{x_k\}) = J(1, T_2, \{x_k\})/A^2$, and hence the selection of $T_2$prep echo times does not depend on $A$ or $B$, but only on the $T_2$ values of interest.

$J(1, T_2, \{x_k\})$ was numerically minimized for $T_2$ values of interest from 45 ms to 60 ms, for $K=4$ and $K=28$. For $K=4$, this yielded a tri-modal distribution with $T_2$prep echo times of 0, 49 ms (sampled twice) and $\infty$. For $K=28$, the distribution of $T_2$prep echo times of 0 sampled six times, 53 ms sampled fourteen times and $\infty$ sampled 8 times. This kind of tri-modal distribution is consistent with the bi-modal distribution in (36) for the two-parameter $T_2$ model, and the tri-modal one in (37) for the 3-parameter $T_1$ model.

Furthermore, if instead of the $\infty$ $T_2$prep echo time, one could only sample a maximum finite value of 90 ms, the distributions changed to 0, 32 ms (sampled twice), and 90 ms for $K=4$; and 0 (sampled 6 times), 33 ms (sampled 14 times), and 90 (sampled 8 times) for $K=28$. In this case, the variance of the $T_2$ estimate increased by 5.4-fold and 5.5-fold for $K=4$ and 28, respectively. A direct comparison for $K=4$ also showed that $T_2$prep echo times of $[0, 25, 50, 90]$ had 5.6-fold higher variance compared with $[0, 25, 50, \infty]$. These results indicate that sampling the $\infty$ $T_2$prep echo time improves the precision of the fit compared with sampling a large but finite $T_2$prep echo time.

We note that this derivation is based on the least squares estimation, which has a one-to-one correspondence with a Gaussian noise model in the images. However, the noise in the magnitude images is Rician, which can be well-approximated by Gaussian noise for images with sufficient SNR (34), an assumption that may not
hold for $\delta_{SAT}$ images. This may lead to a model mismatch and an apparent bias in $T_2$ estimates, although this was not observed in our study.

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