Relaxation Time Measurements in NMR Imaging
Part I: Longitudinal Relaxation Time

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Relaxation time measurements are important in magnetic resonance imaging. This paper discusses the need for creating calculated relaxation time images and it reviews current practices in the field. Imaging techniques based on inversion recovery, partial saturation, and variable-tip-angle experiments, as well as single-shot methods that employ stimulated echoes or multiple-readout pulses are considered. Virtues and limitations of each method are reported.

INTRODUCTION

In this article and a subsequent one, we review the methods commonly used for relaxation time measurements in hydrogen (proton) magnetic resonance imaging (MRI). The advantages and disadvantages of each technique are discussed and common problems are presented. Readers are expected to have a basic knowledge of NMR theory and to be conversant with the fundamental aspects of a conventional two-dimensional, Fourier imaging experiment, although more elaborate details are explained where necessary. Prior knowledge of relaxation processes is also assumed; as their detailed descriptions, the factors on which they depend, and the biomedical implications of relaxation time values can be found in relevant texts (1-5).

The measurement of relaxation times is common practice in NMR spectroscopy. The spectroscopist normally derives a relaxation time value for each chemically shifted spectral peak over the whole volume. However, there are spins that can have the same chemical environment but subtly different physical surroundings; although they contribute to the same spectral peak, they can exhibit different relaxation characteristics. For example, the relaxation times of water protons in different tissues vary over a significantly wide range (some typical values for the longitudinal relaxation time $T_1$, in human studies at a static magnetic field of 2.35 T, are 570 ms for liver, 700 ms for spleen, and 1,020 ms for skeletal muscle [5]). In such a case, spectroscopic relaxation time measurements of the total water resonance would yield only a weighted-mean

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value. Multi-exponential fitting of the experimental data is possible, but the resolution between
different components can be very low, because a single exponential closely represents the
variation of a multi-exponential decay unless the separate components differ by a factor of more
than three (6).

In contrast, relaxation time measurements in MRI involve the generation of a "calculated"
image, in which each pixel holds the mean relaxation time value of all the spins confined to the
corresponding volume element (voxel). In other words, a "map" is produced of the distribution
of relaxation times within the object of interest. The price to pay for this extra spatial
information is that the chemical shift resolution is lost (at least in conventional imaging methods).
Note that calculated relaxation images should not be confused with "weighted" relaxation images.
The latter are conventional MR images acquired using specific sets of imaging parameters (for
example, the echo time [TE] or the repetition time [TR]) so that the contrast depends on one or a
combination of the relaxation times of the sample. Figure 1 demonstrates the different
approaches to relaxation time measurement in spectroscopy, to relaxation-weighted images, and to
relaxation time maps.

Figure 1. (A) Spin-echo image of a phantom consisting of three tubes of distilled water, doped
with different concentrations of copper sulfate to give different $T_1$ and $T_2$ values. The sequence
was performed with a long repetition time ($TR = 5,000$ ms) and a short echo time
($TE = 30$ ms), so that the contrast depends mainly on proton density. (B) A series of inversion
recovery spectra taken from the same phantom for a range of inversion times ($12 - 12,800$ ms).
One resonance line, that of water protons, is resolved and a mono-exponential fit of the signal
intensities assigns a $T_1$ of 440 ms to the water. (C) A $T_1$-weighted spin-echo image of the
phantom ($TR = 800$ ms; $TE = 30$ ms) reveals the $T_1$ differences between the three tubes. The
shorter the $T_1$, the higher the signal intensity. (D) $T_2$-calculated image of the phantom (by
the two-point partial saturation method as described later in the text). Each pixel holds the $T_1$
value of the corresponding pixel in the conventional image. The $T_2$ values for the three tubes
are 890 ms (top), 425 ms (bottom left), and 310 ms (bottom right).
The finite volume of the imaging voxel, however, suggests that even relaxation time maps can suffer from partial volume effects. This is the case when the imaging voxel corresponds to an area that contains tissues with a range of relaxation time values. Although a multi-exponential decay should be expected, only the weighted-mean value is assigned to the imaging voxel. When small structures are involved, measurements could even be impaired, an example being the optic nerve with its surrounding orbital fat (7). A diagram of the partial volume effects in this case is shown in Fig. 2. For simplicity, we have neglected the misregistration of the fat signal relative to water that results from their chemical shift difference. This artifact would be expected to make partial volume effects even more profound (depending on the static and gradient field strength). As the spatial resolution is increased, partial volume effects diminish, affording more accurate measurement of relaxation times (provided the signal-to-noise ratio [S/N] remains the same, e.g., because of increased signal averaging or better sample-receiver coupling). MRI microscopy studies on rat kidneys, for example, have revealed five zones of tissue with distinctly different relaxation characteristics; conventional MRI distinguishes only two regions (8).

![Diagram of partial volume effect for the optic nerve and orbital fat.](image)

Figure 2. Diagram of partial volume effect for the optic nerve, a small structure surrounded by orbital fat. For simplicity, only the pixel area is considered, although the whole voxel is involved. (A) Low spatial resolution image matrix. The nervous tissue corresponds to the four central pixels, i.e., A[2b], A[2c], A[3b], A[3c], which, however, also contain some orbital fat. The overall intensity of each individual pixel is, therefore, the weighted mean of the contributing fat and nervous tissue signals. When the spatial resolution is increased, as shown in (B), one can resolve pixels that correspond only to nervous tissue, i.e., B[4d], B[4e], B[5d], B[5e]. In this example we do not consider the misregistration of the fat signal relative to water due to the chemical shift artifact.

Relaxation time maps in MRI are the primary subject matter of this study. After a brief discussion on their justification, this part of the review concentrates on $T_1$-calculated images and on the various conventional techniques used to create them. Here we also comment on limitations, artifacts, corrections, and practical considerations for each method. A subsequent article will focus on MRI methods for the measurement of transverse relaxation times ($T_2$ and $T_2^*$), and the determination of the rotating-frame relaxation time ($T_{1\omega}$).

**WHY MEASURE RELAXATION TIMES IN MRI?**

Much of the interest in tissue relaxation times has stemmed from the early observation of elevated $T_1$ and $T_2$ values in tumorous tissues of experimental animals (9, 10). Since then, the need for relaxation time measurements in proton MRI has become even more profound; the major reasons are detailed here.
Tissue Characterization and Quantitation

Relaxation time maps have been used to characterize tissue in various circumstances, one obvious case being the differentiation between fat and the rest of the tissues on the basis of fat tissue's markedly shorter $T_1$. Thus, calculated $T_1$ images have been used, for example, to assess the percentage of fetal fat (both subcutaneous and intra-abdominal) with respect to other fetal tissue in normal, as well as diabetic, pregnant women (11). In studies of head and neck cancer, $T_2$ maps have been employed in a computer algorithm to automatically demarcate the boundary of the tumor and thus to identify the target volume for radiotherapy treatment (12).

Contrast Manipulation in MRI: Pulse Sequence Optimization and Synthetic Images

Contrast on an MR image can be manipulated to depend on numerous parameters, especially relaxation times (13). If the relaxation times are known, then the imaging sequence and its timing parameters (such as repetition, echo, or inversion time) can be chosen to give an image with the desired contrast and hence to create the optimum imaging protocol to detect pathology in the shortest possible scan time (14). Parameter optimization also can be critical in sequences, such as short inversion time inversion recovery (STIR) (15), which exploit the $T_1$ relaxation time differences between fat and water protons to completely suppress the signal from fat. Efficient fat-suppression when using STIR can be ensured only when the $T_1$ of fat is known before the experiment begins. A similar example is the long inversion time inversion recovery sequence, in which the inversion time is chosen to null the signal from cerebrospinal fluid, which degrades the brain image by motion artifacts or by partial volume effects (16).

Contrast in MRI can be further manipulated by the use of synthetic images. Given the proton density and the relaxation time values, synthetic images can be generated for arbitrary timings in any pulse sequence, without requiring additional imaging time, thus allowing a rapid retrospective optimization of contrast through interactive control of the sequence and the imaging parameters (17).

Relaxation Times as Markers of Other Physical Parameters

Because paramagnetic centers in a solution directly affect the relaxation processes of the solvent (18), relaxation time measurements can be used to detect their pathological presence and measure their concentration in several clinical situations. For example, proton $T_1$ and $T_2$ relaxation maps have been used to obtain quantitative estimates of iron concentration in such liver conditions as transfusion iron overload and hemochromatosis (19, 20). They also have been used to determine the ferritin content of brain tissue (21). $T_1$ relaxation maps have been used in Fricke dosimetry to aid in electron and photon therapy planning (22).

Relaxation rates, particularly $T_1$, depend on temperature, and $T_1$ maps can encode information relating to temperature distribution (23). Some studies suggest that the temperature resolution obtained (1 - 2 °C for a spatial resolution of 4 - 5 mm and 1 s scan time) using calculated $T_1$ images should be sufficient for noninvasive temperature mapping in clinical hyperthermia treatment of hypoxic tumors (24, 25).

There also is potential for the use of relaxation time maps to spatially encode any variation in any other physical processes that affect relaxation. For example, $T_2$-calculated images have been shown to correlate with pore size variations in brine-saturated cores (26), and a high correlation between the rise in intraocular pressure and $T_2$ relaxation times has been found in studies of endocrine orbitopathy (27).

Diagnostic Information

It should be clear that relaxation times have a complex, leading role in routine MRI and a potential to become even more important. However, the possibility of reaching a diagnosis based only on relaxation time maps is often regarded with skepticism, as most clinical studies indicate a
large spread in relaxation time values for normal and diseased tissues (28). When performed over a period of time and on the same patient, however, relaxation measurements are sensitive, and they can be correlated directly to specific pathologies. For example, the differential diagnosis of brain disease can be aided by relaxation time measurements when conventional imaging fails to distinguish them (29). Relaxation time maps also are important in evaluating the effectiveness of therapy (30). Finally, knowledge of relaxation times also is required for correct image interpretation, especially when images obtained at different static field strengths are to be compared.

**T₁ MEASUREMENTS IN MRI**

The most commonly used methods for generating T₁ maps are based on the basic pulse sequences used for T₁ measurements in spectroscopy: progressive saturation (PS) and inversion recovery (IR). These radio-frequency pulse sequences can be combined with several imaging techniques, spanning from the very first point- and line-scan methods to the more contemporary Fourier methods and fast imaging regimes such as echo-planar and low-tip-angle, gradient-recalled echo imaging. Here, we describe the principle of each technique. As an example, incorporation into the common spin-echo, two-dimensional (2D) Fourier imaging regime will be assumed. Alternative imaging methods for determining T₁ also are reviewed. These include stimulated echo (STE) imaging and variable-tip-angle and multiple-readout imaging regimes. The latter have recently drawn much attention, primarily because S/N can be traded off for shorter imaging times.

**Progressive Saturation and Saturation Recovery**

The first published calculated T₁ image (31) was generated using progressive ("partial") saturation (PS) (32). This sequence as incorporated in 2D Fourier transform spin-echo imaging is shown in Fig. 3. The initial 90° pulse perturbs all of the magnetization within the selected slice into the transverse plane. This transverse magnetization then precesses during the time interval TE and relaxes exponentially with a time constant T₂, as the 180° pulse refocuses any dephasing due to field inhomogeneities. Longitudinal relaxation occurs during the interval TR until the next sequence repetition, and the longitudinal magnetization recovers toward its thermal equilibrium value with a time constant T₁. If the next 90° pulse is applied after a relatively long time (≥ 5 T₁), the longitudinal magnetization has been allowed to recover completely during the intermediate period. However, if the repetition time of the sequence is short, only a fraction of the thermal equilibrium magnetization recovers. Therefore, the transverse magnetization generated by the subsequent 90° pulse, as well as the acquired signal, is a function of T₁ and TR. After a few sequence repetitions, a steady state is reached and the signal strength (Sₛ) for each pixel in the image is given by the expression

\[ Sₛ = CMₑ \exp(-TE/T₂)(1 - \exp(-TR/T₁)) \]  

[1]

Mₑ is the net magnetization at thermal equilibrium, and C is a dimensionless constant representing the gain of the receiver circuit. The first exponential term in Eq. [1] refers to the transverse relaxation during TE: had the 180° been omitted in a gradient-recalled version of the sequence, this decay time constant T₂ would have been replaced by the effective transverse relaxation time T₂*. The second exponential term accounts for the partial relaxation of the magnetization in the interval TR between successive 90° pulses. In the above analysis we assume T₂* = (TR – TE); that is, any residual transverse magnetization is completely dephased before the next sequence repetition. Furthermore, T₁ effects are neglected during the time between the 90° and the refocusing 180° pulses (see General Considerations). Note that very short T₁ values (comparable to TE) cannot be measured accurately; this magnetization is greatly relaxed toward its thermal equilibrium value before data collection. If all pulses are slice selective (as shown in Fig. 3), the effect of the sequence is confined within a single slice, and data from several slices can be obtained within the repetition time by following the same regime using different frequency offsets for all pulses. However, there is a limit to the number of slices that can be accommodated if the
repetition time must be relatively short to obtain a data point early in the relaxation curve, especially when we wish to interrogate a short $T_1$ value.

![Diagram of a 2D Fourier transform spin-echo pulse sequence](image)

**Figure 3.** Partial or progressive saturation in a 2D Fourier transform spin-echo pulse sequence. The $T_1$ map generation requires at least two repetitions of the imaging sequence with different values for TR. TR is kept constant.

If several images are obtained with different values of TR, the value of $T_1$ for each pixel can be calculated independently of the spin density and the transverse relaxation. This normally involves a nonlinear, multiparametric, least-squares fit through iteration, which, considering the large number of pixels (65,536 for an image of 256 x 256 resolution), can be a time-consuming process, although special fast algorithms have been developed (33). Rapid non-least-squares processing techniques also have been described in the literature, although they generally sacrifice some accuracy for speed (34, 35).

At this point we should mention that several publications incorrectly refer to progressive (or partial) saturation as saturation recovery (SR). That method, as presented in the early days of NMR spectroscopy (36), involves an initial burst of radio-frequency pulses to completely saturate the system; that is, to "zero" the net magnetization. Then, after a time $T$, a 90° pulse samples the amount of relaxed magnetization and the final signal is given by an expression similar to Eq. [1]. The delay time $T$ is used instead of the repetition time TR. The time interval $T$ can be made as short as desired (the only limitation is the switching of electronics), so theoretically there is no lower limit to the accurate measurement of $T_1$. However, many medical applications use the partial or progressive saturation method instead of SR, mainly because the initial burst of the radio-frequency field can dissipate a considerable amount of energy into the subject, and the extra $T$ delay prolongs the overall imaging time. The problem of excessive energy deposition can be overcome using a version of the SR sequence in which the saturating burst of pulses can be substituted by a single 90° pulse to tip the spins into the transverse plane, followed by a pulsed magnetic field gradient to completely dephase ("spoil") the transverse magnetization or by just allowing a long delay relative to $T_1^*$ (6, 37).

**Inversion Recovery**

Another popular method of data acquisition for creating $T_1$ maps is based on the inversion recovery (IR) sequence (38). The pulse diagram for a conventional spin-echo 2D Fourier transform imaging version is shown in Fig. 4. This method uses an initial 180° pulse to invert the spin population within the selected slice, which is then left to relax with the time constant $T_1$,
At TI a 90° pulse "reads" the relaxed magnetization. The final signal \( S_{in} \) is proportional to the fraction of the magnetization that has managed to relax during the inversion time interval TI:

\[
S_{in} = CM_0 \exp(-TE/T_2)[1 - 2 \exp(-TI/T_1)]
\]  \[2\]

The first exponential term in Eq. [2] refers to the signal decay due to transverse relaxation during TE; the latter accounts for TI relaxation during TI. Again, as in Eq. [1], we assume \( T_1^* \ll (TR - TE - TI) \), so that transverse magnetization is completely dephased before the next repetition of the sequence. And again, T1 effects are neglected during the time between the 90° and the refocusing 180° pulses (see General Considerations).

Figure 4. Inversion recovery in a 2D Fourier transform spin-echo pulse sequence. The TR, map generation requires at least two repetitions of the imaging sequence with different values for TI. TE is again kept constant.

For Eq. [2] to hold, the TR of the sequence must be long enough for the perturbed magnetization to return to its thermal equilibrium value prior to the next inversion pulse. Practically, this means that a repetition time of at least five times the longest \( T_1 \) should be ensured (\( \sim 99\% \) recovery). However, this requirement is rarely met in the imaging context, as the imaging time would be unacceptably long (e.g., \( TR = 10 \) s in vivo). In practice, the repetition time needs to be relatively short, so Eq. [2] is modified to account for the partial recovery of the magnetization in the time interval between the read 90° pulse and the next sequence repetition (39). Thus the observed signal for each pixel in the image is given by the expression

\[
S_{ir} = CM_0 \exp(-TE/T_2)[1 - 2 \exp(-TI/T_1) + \exp(-TR/T_1)]
\]  \[3\]

From now on, when we refer to the IR experiment, Eq. [3] is always assumed unless otherwise stated.

If several images are obtained with different TI (while other sequence timings are kept the same), then a nonlinear, multiparametric, least-squares fit for each pixel of the image matrix would again yield a \( T_1 \) map. Similar processing algorithms can be used, as in the case of the saturation methods. The IR sequence also can function in a multislice mode in the same fashion as in the PS experiment. Other more complicated and more time efficient multislice schemes have been proposed (40, 41).

The IR method often is preferred because it exhibits a wider dynamic range than do the saturation techniques; the magnetization initially is inverted and it relaxes starting from a negative value. This very fact of negative signals, however, can induce a fundamental difficulty, known as
contrast reversal (42). In MRI experiments, data are generally presented as magnitude images to avoid the need to correct phase shifts induced by pulse sequence timing errors, phase delay of electronic circuits, gradient ramping and eddy currents, static field inhomogeneity, and moving spins. In such a magnitude image, negative signal intensities are inverted. Figure 5 shows the actual relaxation curve of the magnetization after an inverting 180° pulse and how this will appear when only the modulus of the intensity is considered. It is apparent that the negative signal from a long $T_1$ component cannot be distinguished from positive signals of the same magnitude given by samples with shorter $T_1$ values. Several methods have, however, been used to restore signal polarity in IR images. A first approach is to search for the null point of the magnetization for each pixel in a set of IR images acquired with different inversion times (43). Because at least four IR images are required, this technique cannot be incorporated within two-point or one-shot $T_1$ measurement regimes. Alternatively, the sign information can be recovered if one considers and corrects for the phase shifts of the data prior to the $T_1$ map reconstruction.†

![Figure 5](image_url)

**Figure 5.** Relaxation curves for longitudinal magnetization after a 180° inverting pulse. The dashed and solid lines correspond to the magnitude representation of the relaxation curves for two components with different $T_1$ values ("short" $T_1 = 200$ ms; "long" $T_1 = 500$ ms). The dotted lines show the negative part of the curves when sign information also is considered. Consider, for example, that we observe the system at an inversion time $B$, when the long $T_1$ component gives a magnitude signal much lower than the short $T_1$ component. However, if we observe the system at time $A$, the contrast is reversed.

Several studies have provided a comparison between saturation methods and the IR experiment in terms of their achieved precision in the $T_1$ calculation within the same total experimental time; their authors suggest optimal parameter settings (47-49). When systematic errors, such as pulse imperfections and slice profiles are not considered, IR experiments, with repetition times of about double the maximum estimated $T_1$, and $T1$ values linearly spaced in time, give better results than saturation sequences do (48). However, the prolonged imaging and processing times have led to the development and adoption of two-point measurement techniques that often employ hybrid, more efficient pulse sequence schemes, as described below.
Two-Point Measurements and Hybrid Schemes

Longitudinal relaxation time can be derived from only two images using the "intensity ratio" method (50). In this approach, two different repetition times (if PS is considered), or two different values for the waiting time T (for the SR sequence), or two different inversion times (for the IR sequence) are necessary. The echo time, TE, and all other parameters are kept constant for both imaging experiments. For PS, the ratio of intensities for any given pixel in the image matrix is given by

$$\frac{S_a}{S_b} = \frac{1 - \exp(-TR_a/T_i)}{1 - \exp(-TR_b/T_i)}$$  \[4\]

$S_a$ and $S_b$ are the signal intensities for the two PS images acquired with repetition times $TR_a$ and $TR_b$, respectively. For IR, the corresponding expression is

$$\frac{S_a}{S_b} = \frac{1 - 2\exp(-TI_a/T_i) + \exp(-TR_a/T_i)}{1 - 2\exp(-TI_b/T_i) + \exp(-TR_b/T_i)}$$  \[5\]

$S_a$ and $S_b$ are the signal intensities for the two IR images, obtained with repetition times $TR_a$ and $TR_b$ and inversion times $TI_a$ and $TI_b$, respectively. The most convenient method of generating the $T_i$ map is to refer to a computed "look-up" table, which is a list of the theoretically determined signal ratios for the specific values of repetition or inversion times used in the experiment for various values of $T_i$, using Eq. [4] or Eq. [5], accordingly. Then, the signal ratio for each pixel is calculated and compared with the computed values (51).

It is worth noting that $T_i$ determination can be precise only if the pulse intervals are chosen suitably. In the PS sequence, for example, if the measurements are made too early in the exponential recovery curve, then the intensity ratio becomes insensitive to $T_i$; if the pulse intervals are both long in comparison with the relaxation time to be determined, the intensity ratio tends to unity. Near these limits any noise on the signals introduces large errors in the derived relaxation times. A large ratio of repetition times $TR_a/TR_b$ permits a wide range of relaxation times to be determined, but tends to be more time consuming than a smaller ratio will be. In practice a $TR_a/TR_b$ of four has been found to represent a reasonable compromise (50, 52). In the case of IR, high precision is obtained when one of the experiments is near the null condition (50).

A hybrid two-point measurement scheme has, however, proved most efficient. It was suggested in the early days of NMR imaging (53) and still is the method of choice for many
clinical studies. The method involves a partial saturation and an IR imaging experiment. Then the ratio of intensities for any pixel in the data matrix of the two images is given by

$$\frac{S_{IR}}{S_{PS}} = \frac{1 - 2 \exp(-TI/T_1) + \exp(-TR_{IR}/T_1)}{1 - \exp(-TR_{PS}/T_1)}$$

[6]

$S_{IR}$ and $S_{PS}$ are the signal intensities for the IR and PS images with repetition times $TR_{IR}$ and $TR_{PS}$, respectively. The two sequences can form two completely different experiments, or they can be interleaved within the same sequence. The latter is preferred, because it compensates for any misregistration due to involuntary movement or shift in electronics during the different steps of the phase-encoding procedure. A computed look-up table is again used for the generation of the $T_1$ map. In theory, the inverse ratio $S_{PS}/S_{IR}$ is equivalent for the purpose of $T_1$ measurement; however, it can create practical computational problems as it approaches infinity for combinations of $TI$ and $T_1$ where the IR signal is zero. This hybrid PS-IR method has been shown to be more efficient than other two-point measurement schemes for determining $T_1$ within a wide range of possible values (52). Optimal parameter settings also have been suggested. For example, to measure $T_1$ within 120-1,200, 150-1,500, or 200-1,800 ms, the optimum $TI$ should be about 280, 400, or 500 ms, respectively; the same optimum $TR_{IR}/TR_{PS}$ of 2.5-3.0 would apply to all three bands (52). Figure 6 is an example of a $T_1$ map of mouse brain generated by the hybrid two-point PS-IR method.

![Figure 6](image)

**A**

**B**

**C**

Figure 6. Coronal slice of the brain of a live normal mouse at 4.7 T. (A) Partial saturation spin-echo image with $TR = 2,000$ ms and $TE = 32$ ms. (B) Inversion recovery image, with $TI = 300$ ms, $TR = 5,000$ ms, $TE = 32$ ms. (C) Calculated $T_1$ image using the two-point hybrid PS-IR method. The images were acquired using a surface coil placed around the head.

**Variable-Tip Angles**

$T_1$ maps can also be generated by using a variable-tip-angle pulse during the imaging experiment. In this method, a pulse of tip angle $\theta^\circ$ is used to perturb the magnetization, which is then left to partially relax back to its thermal equilibrium value during the short repetition time $TR$. As the excitation pulse is generally other than 90°, only a fraction of the thermal equilibrium magnetization is "tipped" into the transverse plane. This transverse magnetization is then a function of both the pulse tip angle $\theta^\circ$ and the amount of longitudinal relaxation that has occurred during the time interval $TR$ (54). In this case, the application of a 180° refocusing pulse to form
a spin echo cannot be used, because such a pulse also would invert the magnetization that has remained along the longitudinal axis. Instead, an echo is formed through the use of gradients. This radio-frequency pulse sequence can then be incorporated into any imaging regime, as in Fig. 7 (55). The transverse relaxation during $TE$ is now described by the effective transverse relaxation time constant $T_1^*$ and the signal intensity $S_n$ for any pixel in the data matrix is given by

$$S_n = CM_e \exp(-TE/T_1^*) \frac{\sin \theta [1 - \exp(-TR/T_1^*)]}{1 - \cos \theta \exp(-TR/T_1^*)}$$  \hspace{1cm} [7]$$

This assumes that pulses are applied along the same axis and that a steady state has been reached, which can generally be achieved within the first few sequence repetitions (56). $TR \gg T_1^*$ also is assumed, so that the transverse magnetization is completely dephased prior to the next sequence repetition. For a pulse of tip angle $\theta = 90^\circ$, Eq. [7] reduces to Eq. [1], which describes the progressive saturation experiment, with the exception of the time constants for the transverse relaxation. One would, therefore, expect that the two methods are similar, with the fundamental exception that Eq. [7] can be rearranged to allow linear data analysis to be employed for the $T_1$ calculations:

$$\frac{S_n}{\sin \theta} = \exp(-TR/T_1^*) \frac{S_n}{\sin \theta} + CM_e \exp(-TE/T_1^*)[1 - \exp(-TR/T_1^*)]$$  \hspace{1cm} [8]$$

Several images are acquired with the same $TR$ but with different values for the pulse tip angle $\theta$. Following Eq. [8], the plot of $S_n/\sin \theta$ against $S_n/\tan \theta$ is a straight line with a slope of $\exp(-TR/T_1^*)$. Because the rest of the parameters, such as spin density and transverse relaxation constant, affect only the intercept of the linear plot, they do not interfere with the calculation of $T_1$.

Figure 7. Variable-tip-angle, 2D Fourier transform gradient-recalled echo pulse sequence. A randomized spoil gradient pulse ensures complete dephasing of the transverse magnetization prior to the next sequence repetition. The $T_1$ map generation requires at least two repetitions of the imaging sequence with different values for the tip angle $\theta$ of the excitation pulse. $TE$ is kept constant.

Studies of sequence parameter optimization have shown that two-point measurements using only two images acquired at two different tip angles can be even more precise than a multiple-point measurement considering the same overall repetition time (57). Additionally, simulation and experimental results suggest that the optimum sequence parameters should involve a pair of well-separated tip angles ($20^\circ$ and $100^\circ$) and a short repetition time, such that $TR \leq T_1$. As a result, the method is quite fast, although care should be taken so that the transverse magnetization is completely spoiled before the next sequence repetition (if $T_1^*$ is comparable to the repetition time, an additional, randomized spoiling magnetic field gradient also should be employed). The variable-tip-angle method also has been shown to be at least as efficient as its most closely related
technique, progressive saturation (57). However, some limitations should be considered. The most important probably is that because the sequence cannot use a 180° refocusing pulse for the echo formation, the final signal intensity can be prohibitively poor in a relatively inhomogeneous static magnetic field. Errors also can arise in the calculation of the pulse tip angles, especially when there is a variation of the tip angle across the slice thickness.

**Single-Shot Techniques**

All methods described so far require more than one imaging experiment to generate the calculated $T_1$ image. This is probably the most important limitation of $T_1$ mapping because at least twice the imaging time is required. It is worth noting that sequences such as the hybrid PS-IR are often already performed in most clinical examinations to get images with a variable $T_1$ contrast; in these cases calculation of a $T_1$ map would give additional information without requiring extra imaging time. Nevertheless, single-shot $T_1$ measurements would be most desirable. Several techniques can generate $T_1$ maps using information from only one sequence repetition.

One group of single-shot $T_1$ measurement methods involves stimulated echo (STE) imaging (58-60). A typical STE pulse sequence is shown in Fig. 8. The magnetization initially is tipped into the transverse plane by the first 90° pulse and it dephases during the time interval $TE/2$. At the same time, phase encoding is performed. The following 90° pulse causes half the magnetization to be stored in a plane parallel to the longitudinal axis, preserving its acquired phase information; the other half of the magnetization rephases to form an echo after a further time $TE/2$. This echo is usually called the primary echo (PE). The signal intensity for any given pixel in the PE image matrix is given by

$$S_{PE} = \frac{1}{2} CM_0 \exp(-TE/T_1)$$

which is the same as in an equivalent, conventional spin-echo experiment except for the factor of one-half. The other half of the magnetization that has been stored along the longitudinal axis is then brought back into the transverse plane by the application of a third 90° pulse and rephases to form an echo after a further time $TE/2$. This is commonly called the stimulated echo. During the intermediate time interval $TM$ the stored magnetization experiences only longitudinal relaxation. If $TM$ is too long ($\geq 5 T_1$), practically all spins relax back to thermal equilibrium, and by the time the third 90° pulse is applied no stored magnetization is left to form a stimulated echo. Therefore, the signal intensity for any pixel in the STE image depends not only on $T_1$ relaxation during $TE$ but also on the $T_1$ relaxation during the interval $TM$:

$$S_{STE} = \frac{1}{2} CM_0 \exp(-TE/T_1) \exp(-TM/T_1)$$

Equations [9] and [10] assume that the pulse sequence repetition time is long enough to avoid additional $T_1$ dependence via partial saturation. Then, the ratio of STE signal intensity to the intensity of the PE image is a direct measure of $T_1$ (61):

$$\frac{S_{STE}}{S_{PE}} = \exp\left(\frac{-TM}{T_1}\right)$$

The major advantage of this two-point $T_1$ technique is that only one imaging experiment is required; both the primary and the stimulated echo are collected within one sequence repetition. The two data sets also are inherently interleaved, thus reducing the effect of motion or drift in electronics on the accuracy of the $T_1$ measurements. However, the signal intensities are only half the intensity of the conventional spin echo. This poorer S/N can lead to larger errors in the $T_1$ measurements, and four times as many averages are required to double the S/N in an NMR image (62). An example of a $T_1$ map generated using the primary and stimulated echoes of an STE sequence is shown in Fig. 9.
Figure 8. In the STE pulse sequence, the primary echo, formed at a time $TE/2$ after the second 90° pulse, is a spin echo with half the signal intensity of a conventional spin echo formed using a 180° refocusing pulse. The signal intensity of the stimulated echo, formed at a time $TE/2$ after the third pulse, decreases exponentially with $T_1$ as $TM$ increases. Generation of the $T_1$ map requires both primary and stimulated echoes, which are obtained within the same sequence repetition.

Figure 9. Transverse image of the brain of a normal human volunteer at 0.5 T. (A) PE image of an STE sequence, $TE = 120$ ms. (B) STE image from the same pulse sequence, $TM = 150$ ms. (C) $T_1$ map derived from the PE and STE images according to Eq. (11).
Perhaps the most interesting advantage of STE imaging is that the technique can be manipulated to give more than two points in the relaxation curve within only one imaging experiment, thus allowing the study of possible multi-exponential relaxation behavior within a reasonable imaging time. For this purpose, the third 90° pulse in Fig. 8 is split into a number of small-tip-angle pulses that partially sample the stored magnetization at different TM intervals. Each read pulse reduces the residual stored longitudinal magnetization (and hence the magnitude of the next stimulated echo) by a factor of the cosine of the tip angle. We can achieve the same tip angle dependence for all the stimulated echoes by properly adjusting the tip angle of each read pulse, although this requires very good B₀ field homogeneity. Detailed calculations show that, ideally, the tip angles should increase from small values to reach 90° for the last pulse in the series (63, 64). An alternative approach is to set all pulses to have a very small tip angle (about 5°), and in the case of such a small angle the cosine can be approximated by 1 (63). The lower the tip angle of the read pulse, however, the poorer the S/N of the resulting image. Another important consideration is that use of such a multipulse sequence can form several different and unwanted echoes during each acquisition interval. For example, spin echoes of previous stimulated echoes, and stimulated echoes of previous spin echoes can be generated, giving rise to "ghost" artifacts that not only degrade the image quality but also can lead to regional alterations in the signal intensity. Phase-cycling procedures (which involve extra signal averaging) and systematic application of magnetic field gradients can suppress unwanted signals and give artifact-free stimulated echo images (65).

Another group of single-shot methods for producing T₁ maps is based on the principle of using multiple-readout pulses to sample the longitudinal magnetization at the transient region as it evolves toward a steady state (66). (Note that the techniques described so far consider only the steady-state condition for the magnetization and avoid the transient decay toward this state.) These multiple-readout sequences involve a series of evenly spaced readout, low-tip-angle (θ° < 90°) pulses. Each θ° excitation pulse forces some of the longitudinal magnetization into the transverse plane and produces a signal proportional to the amount of the longitudinal magnetization before the pulse. This signal is always recorded as a gradient-recalled echo because a 180° refocusing pulse also would invert the magnetization that remains along the longitudinal axis. Between the pulses, which are applied with a short time interval T, the magnetization still relaxes with T₁. However, the apparent overall decay toward a steady state is characterized by an effective relaxation time T₁eff, which is related to the actual T₁, the pulse tip angle θ°, and the interpulse delay T by

\[ T₁_{eff} = \frac{T}{T/T₁ - \ln(\cos\theta)} \]  \[\text{[12]}\]

The tip angle θ° must be less than 90° so that the logarithm of \(\cos\theta\) is permissible in Eq. [12]. Other assumptions include the complete spoiling of the transverse magnetization prior to the application of the next readout pulse, which can be ensured by \(T > T₂\), or by application of an appropriate spoiling field gradient pulse. It is apparent that the train of low-tip-angle readout pulses is used both to perturb the longitudinal magnetization from the thermal equilibrium condition and to sample it consecutively as it gradually decays toward a steady-state value (66, 67).

To increase the dynamic range of the experiment, a saturating or inverting pulse can be used to prepare the magnetization at some starting value (68-70). The readout pulse train samples the magnetization as it relaxes exponentially from zero or a negative value, respectively, toward a steady state. Most applications of the method include an initial 180° inverting pulse, because in this case the magnetization is sampled over a wider range of values (in the same fashion that the IR experiment exhibits a wider dynamic range than does the PS). The evolution of the longitudinal magnetization in all different versions of the preparation part of the sequence is characterized by the same effective relaxation time \(T₁_{eff}\) as it converges toward the same equilibrium value. The value of this equilibrium magnetization depends on the actual \(T₁\), as well as on the tip angle \(θ°\) and the interpulse delay \(T\); it is given by an expression equivalent to Eq. [7]. A pulse sequence diagram and a schematic description of the recovery of longitudinal magnetization for the multiple-readout sequence are shown in Fig. 10.
Figure 10. (A) Multiple-readout, 2D Fourier transform, gradient-recalled pulse sequence. The 180° preparation pulse can be omitted or substituted with a 90° pulse. TE is kept constant throughout the train of readout pulses; the randomized "spoil" magnetic field gradient pulse ensures complete dephasing of the transverse magnetization before the application of the next readout pulse. The T₁ map is generated using all the echoes in the readout train, which are obtained within the same sequence repetition. (B) The recovery of the longitudinal magnetization during the course of the multiple-readout pulse sequence (a) when the preparation pulse is omitted, (b) when the preparation pulse is 90°, and (c) when the preparation pulse is 180°. The calculations assume a T₁ of 500 ms, a T₂ of 20 ms between the preparation pulse and the readout train, 20 readout pulses of 20° tip angle and T = 80 ms, and a repetition time of 2,300 ms. The magnetization gradually approaches a steady state; the steps in the curves are due to the readout pulses, which bring some of the longitudinal magnetization into the transverse plane. The greatest change in the longitudinal magnetization (the dynamic range of the experiment) is obtained at (c), when the preparation pulse is 180°.
As several readout pulses are performed during each sequence repetition, a full reconstruction of the decay curve is possible and \( T_1 \) can then be calculated using Eq. [12]. When the pulse tip angle \( \theta^* \) is not known accurately, a three-parameter fit of the data can give a \( T_1 \) map as well as the spatial distribution of the radio-frequency field (67). In the case of the inverting preparation pulse, signal polarity should be restored prior to \( T_1 \) calculations. The simple two-point algorithm described above can be used when the inversion recovery and the partial saturation images required are substituted by the first and the last images, respectively, in the readout train (44).

Several studies have been published on the optimization of the multiple-readout sequence parameters (71 - 73). Large pulse tip angles increase S/N in the resulting images, but low tip angles are required to maintain the maximum dynamic range and to minimize the error in the calculated \( T_1 \). As a good compromise, tip angles in the range of 15° to 30° have been suggested (72). The calculated value of \( T_1 \) is sensitive to the precise value of the tip angle only when \( T/T_{1\text{ref}} \) is small. An optimization of the interpulse delay \( T \) through iterative processes suggests that \( T \) should be in the range of 70 - 100 ms, for accurate measurements of \( T_1 \) values ranging from 150 to 900 ms (72). Experimental results show that accurate measurements can be obtained for a range of \( T_1 \) values when the interpulse delay is chosen to sample points spread well over the longest expected relaxation curve (71).

It is apparent that the multiple-readout methods sacrifice some S/N to obtain a complete characterization of the recovery curve. However, this extra information can be invaluable when a multi-exponential relaxation decay is suspected, because of actual multi-exponentiality in the microscopic tissue environment or because of partial volume effects. Comparative studies have shown that within the same total imaging time, multiple-readout methods can produce calculated \( T_1 \) images with S/N comparable to that of \( T_1 \) maps generated by conventional multiple-point methods, such as IR (74). In the single-shot methods, the extra imaging time is used for signal averaging, and not for sampling more points in the relaxation curve, thus it is possible to trade off \( T_1 \) map S/N to reduce the overall imaging time, if so desired. Nevertheless, in clinical examinations a conventional image with an acceptable S/N is also generally required for morphological inspection. To avoid the need to perform additional standard experiments for this purpose, one could take a weighted sum of all the images produced by the multiple-readout sequence and thus generate a composite image of clinical quality (67, 75). Another approach involves modifying the sequence so that the last readout pulse is adjusted to give an effective tip angle of 90°, yielding an image with maximum possible S/N (76).

**General Considerations**

The first step toward more accurate \( T_1 \) measurements is the use of elaborate signal calculations, derived with less approximations. For example, Eqs. [1] and [3] for the signal intensity of the SR and IR spin-echo experiments, respectively, assume that the \( T_1 \) is very long compared to \( TE \). Therefore, at the time of the application of the refocusing 180° pulse, effectively no longitudinal relaxation has occurred, and all magnetization is in the transverse plane. However, if the \( T_1 \) is comparable to \( TE/2 \) and if some of the magnetization has relaxed during this time, the refocusing 180° pulse would invert any longitudinal magnetization, thus leading to a more complicated expression for the signal intensity (77 - 79).

Another important factor that can induce substantial inaccuracies in \( T_1 \) measurements is the effect of magnetization transfer contrast, i.e., the reduction of the longitudinal relaxation time of certain tissues when off-resonance pulses are applied (80). Multislice imaging can effectively be regarded as off-resonance irradiation, and it has been shown that the signal from tissues in such sequences decreases because of magnetization transfer effects, this reduction in S/N being dependent on the number of slices and other sequence parameters, such as the repetition time (81). Such incidental magnetization transfer effects, however, would not be observed when off-resonance pulses are avoided, as in three-dimensional imaging techniques.

Other factors that can affect the expected signal and thus the \( T_1 \) calculations include hardware imperfections, such as \( B_1 \) field inhomogeneity and imperfect slice profiles. Although in most
clinical examinations modern instrumentation affords only a small percentage variation in $B_i$ field homogeneity in the central imaging volume, the nonuniform excitation field of surface or internal coils is still a major problem. A practical solution would be to use a large, imaging transmitter coil for homogeneous excitation over the imaging volume and a separate surface (or internal) receiver coil for maximum S/N for the volume of interest (82). Alternatively, a map of the $B_i$ field could be used to correct the $T_i$ measurements during postprocessing, although this requires additional experiments. Information about the tip angle distribution could be obtained together with the $T_i$ calculation when a multiple-point method is used and the data are subsequently analyzed in terms of a two- or three-parameter exponential fit, one of the parameters being the pulse tip angle (49, 67, 83). Such an approach would be time consuming when methods such as PS or IR are considered, but could be applied in the multiple-readout sequences (although a rather long processing time may be needed and the nonlinear fitting required might not be sufficiently robust [77]).

A more common solution to the problem of inhomogeneous $B_i$ field, however, is to use specially designed pulses that self-compensate for any $B_i$ inhomogeneity. Such an example is the broad category of composite pulses, initially designed for spectroscopic studies. (For a review, see References 84 and 85.) One should note that although these pulses can be made frequency selective, the resulting slice profile can be far from the ideal rectangular shape. Adiabatic fast-passage pulses also are $B_i$ insensitive. (For a review, see Reference 86.) Such a pulse, achieved by a nonlinear frequency sweep, has been used for inversion in the hybrid two-point PS-IR method to produce $T_i$-calculated images with increased accuracy (87). (It should be noted that although all the pulses in the sequence are likely to be mis-set by the same proportion, this sequence is much more sensitive to errors in the inversion pulse than it is to errors in the other pulses; the latter will affect both halves of the sequence in the same way, and so will not cause any significant change in the signal ratio, Eq. [6].) In current clinical practice, most commonly used are the complex hyperbolic secant pulses, which can create a highly selective spin inversion or excitation, which, above a critical threshold, is independent of the pulse power and hence $B_i$ inhomogeneity (88). The use of a hyperbolic secant 180° pulse for the inversion in the hybrid PS-IR method, as well as in the multiple-readout sequence, has been shown to give increased accuracy in $T_i$ measurements (73, 89). The pulse also can be optimized to produce slice profiles much closer to the desired rectangular shape (90).

In conventional 2D imaging, the slice selection is performed by application of a frequency-selective pulse in the presence of a magnetic field gradient, thus the distribution of tip angles across the slice is expected to be a simple reflection of the spectral "shape" of the pulse. As most conventional pulses exhibit frequency profiles different from the rectangular shape, assuming a uniform tip angle distribution across the slice would generally lead to erroneous $T_i$ measurements or even create an apparent multi-exponential relaxation behavior (77, 91). Slice profile effects can become more pronounced and complicated when multipulse sequences are considered because of the limited magnetization recovery during the interpulse delays (92, 93). Similarly, deviations from the true values considerably increase when adjacent slices overlap (94). It is possible to correct the $T_i$ measurements for the slice profile effects by substituting the nominal pulse tip angle with the appropriate expression derived from integrating through the selective pulse waveform (51, 73, 77, 95) or by estimating an average tip angle value across the slice profile from calibration experiments (96). Direct measurements of the slice profile also can be used when deviations from the theoretical pulse waveform are intended or, because of operating system characteristics, are suspected (77, 93). The slice profile effects could be reduced by reducing the number of slice-selective pulses within the sequence to a minimum, although this would result in single-slice imaging. The problem could be avoided altogether in a three-dimensional imaging sequence, in which "slice selection" is performed by phase encoding, although this again increases significantly the overall imaging time.

Because all methods involve pixel-by-pixel manipulation of more than one image, any spatial misregistration between consecutive images can introduce errors in the final $T_i$ map. The spatial misregistration can be induced either by an imbalance of the encoding gradients or by motion artifacts. The former can be obviated by applying the gradient pulses in exactly the same fashion.
for all images. This is readily applicable to sequences such as PS, IR, or variable tip angle, but might be more difficult with single-shot methods. In a similar sense, mass transfer in general (e.g., flow, diffusion, perfusion) should be considered, especially in single-shot methods for which the reduction in the echo signal due to moving spins becomes more pronounced in the later echoes (60). (For a comprehensive review of the influence of diffusing spins in the echo signal, see Reference 97.) Signal misregistration due to involuntary motion is usually more difficult to avoid but can be reduced by interleaving scans, an inherent benefit of single-shot sequences. Gating of the sequence to a cardiac or respiratory cycle also can be employed, and such cardiac-gated \( T_1 \) maps have been published (98).

**SUMMARY**

Relaxation time measurements are a potentially powerful tool in MRI. The process generally involves acquisition of several images such that a map of the spatial distribution of the relaxation time values can be calculated subsequently. This should not be confused with relaxation-weighted images, where simply the contrast is manipulated to depend strongly on relaxation time values. In this paper we review the methods used to create longitudinal relaxation (\( T_1 \)) maps and we draw attention to some potential sources of inaccuracy in the measurements. We summarize the salient points below.

Some of the methods, such as IR and STE imaging, involve an initial perturbation of the longitudinal magnetization and subsequent observation of the system as it relaxes back to thermal equilibrium. Another group of methods, saturation and variable-tip-angle imaging, force the magnetization into a steady state, whose value depends on longitudinal relaxation. Multiple-readout methods sample the magnetization as it progressively approaches a steady state.

Longitudinal relaxation is generally an exponential process, but often multi-exponentiality also can be expected; therefore it would be most desirable to sample the relaxing magnetization several times during the relaxation process. In conventional methods, such as progressive saturation, IR, or variable-tip-angle sequences, this requires several repetitions of the imaging experiment, resulting in a prohibitively long imaging time. As a consequence, in most clinical examinations only two-point measurements are performed. The single-shot methods, STE and multiple-readout imaging, offer the opportunity to sample several points within the same repetition time. The penalty is a reduction in S/N of the acquired images and a concomitant increase of the stochastic errors in the subsequent \( T_1 \) measurements. However, S/N can be increased by extensive averaging. Thus, when compared with IR, the multiple-readout sequence with a 180° preparation pulse is of similar efficiency within the same overall experiment time. One could conclude that a single-shot method should be preferred in high S/N conditions, for example when the coil and the sample are well coupled (e.g., with surface or internal coils) and the imaging voxel is relatively large. As the field of view is decreased (keeping the spatial resolution fixed) the IR, PS, or variable-tip-angle methods should become more desirable (74). Generally, maximum achievable S/N is required to minimize stochastic errors in the \( T_1 \) measurements, therefore the echo time should be kept as short as possible.

Another point to take into consideration is the potential for problems to arise from the compulsory use of a gradient echo instead of a spin echo in variable-tip-angle and multiple-readout methods. Gradient echoes suffer from an inherent reduction in S/N, depending on the static magnetic field homogeneity, and can exhibit artifacts at the interfaces of spins with different chemical shifts, such as fat and water, additional to the common misregistration of chemically shifted signals in the frequency encode and slice selection direction (99). These artifacts appear as a signal modulation with the echo time \( T_E \), where in the extreme case the signal from voxels that contain both fat and water protons can be canceled completely. The chemical shift effects in the interfaces of fat with other tissues (in both spin and gradient-recalled echo imaging), as well as the partial volume effect, often impair relaxation time measurements in MRI. Recent studies have addressed this problem by combining \( T_1 \) measurement techniques, such as IR and PS, with chemical-shift-imaging sequences to create differential fat and water \( T_1 \)-calculated images
(100-102). However, such combined methods are expected to suffer from long imaging times, because both $T_1$ measurements and chemical shift selection generally require extra imaging experiments.

The extra imaging time generally needed to create $T_1$ maps is often a major problem, especially in clinical routine MRI. The solution seems to lie with the use of high-speed imaging techniques, which offer the additional advantages of allowing relatively motion-independent measurements to be made and the potential for dynamic studies. Thus, the principle of saturation recovery has been incorporated into fast-imaging sequences such as echo planar imaging to yield real-time $T_1$ maps (103). In addition, the magnetization can be prepared by a 180° inverting pulse and a variable waiting period before the application of the fast-imaging experiment, whether it is an echo planar imaging sequence or a fast low-angle shot method (104-106).

Even though spin-lattice relaxation has been considered since the advent of NMR, new approaches to its measurement and manipulation in MRI continue to occupy much of the literature.

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APPENDIX

Acronyms and Abbreviations

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<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>IR</td>
<td>Inversion Recovery</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>PE</td>
<td>Primary Echo</td>
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<tr>
<td>PS</td>
<td>Progressive (&quot;Partial&quot;) Saturation</td>
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<tr>
<td>SR</td>
<td>Saturation Recovery</td>
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<tr>
<td>STE</td>
<td>Stimulated Echo</td>
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<td>STIR</td>
<td>Short Inversion Time Inversion Recovery</td>
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<tr>
<td>TE</td>
<td>Echo Time</td>
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<tr>
<td>TI</td>
<td>Inversion Time</td>
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<td>TR</td>
<td>Repetition Time</td>
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