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Quantitative Cardiac ^{31}P Spectroscopy at 3T Using Adiabatic Pulses

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Abstract

Cardiac phosphorus magnetic resonance spectroscopy (MRS) with surface coils promises better quantification at 3T due to improved signal-to-noise ratios and spectral resolution compared to 1.5T. However, Bloch equation and field analyses at 3T show that for efficient quantitative MRS protocols employing small-angle adiabatic (BIR4/BIRP) pulses the excitation-field is limited by RF power requirements and power deposition. When BIR4/BIRP pulse duration is increased to reduce power levels, T₂-decay can introduce flip-angle dependent errors in the steady-state magnetization, causing errors in saturation corrections for metabolite quantification and in T₁s measured by varying the flip-angle. A new dual-repetition-time (2TR) T₁ method using frequency-sign-cycled adiabatic-half-passage pulses is introduced to alleviate power requirements, and avoid the problem related to T₂ relaxation during the RF pulse. The 2TR method is validated against inversion-recovery in phantoms using a practical transmit/receive coil set designed for phosphorus MRS of the heart at depths of 9–10 cm with 4kW of pulse power. The T₁s of phosphocreatine (PCr) and adenosine triphosphate (γ -ATP) in the calf-muscle (n=9) at 3T are 6.8±0.3s and 5.4±0.6s respectively. For heart (n=10) the values are 5.8±0.5s (PCr) and 3.1±0.6s (γ -ATP). The 2TR protocol measurements agreed with those obtained by conventional methods to within 10%.

Keywords

phosphorus MRS; human heart; human muscle; metabolism; spin-lattice relaxation (T₁); adiabatic pulses; 3 Tesla

Introduction

Localized phosphorus (^{31}P) MRS can measure the high-energy phosphate metabolites, PCr and ATP in the heart. It permits the evaluation of ischemic changes during myocardial stress (1), and ATP turnover through the creatine-kinase (CK) reaction in the normal and failing

human heart (2-4). While most clinical research has been done at a field (B_0) of 1.5 Tesla (T) (1-4), cardiac ^{31}P MRS might benefit from the higher signal-to-noise ratio (SNR) and increased peak separation afforded by 3T (5). However, higher fields present the challenges of: (i) providing adequate B_0 homogeneity to counter the increasing magnetic susceptibility of the body (6); (ii) maintaining radio-frequency (RF) power deposition within regulatory limits; (iii) bandwidth limitations of excitation pulses; and (iv) determining the metabolite relaxation times if metabolites are to be quantified.

In clinical ^{31}P MRS research studies of cardiac metabolites, scan-time and scanner limitations have, to date, invariably necessitated that the magnetization be measured under partially-saturated conditions using surface coils for both excitation and reception (7-9). To estimate the fully-relaxed magnetization (M_0) for metabolite quantification then, spectra must be acquired with a spatially-uniform excitation flip-angle (FA), and the metabolite's longitudinal relaxation time (T1) must be known (10,11). At 1.5T, composite low-angle adiabatic B1-insensitive rotation (BIR4) pulses (12) with phase cycling (BIRP) (13) have provided the uniform FA for surface coil excitation, while T1 was efficiently measured by the dual-angle method from the ratio of the steady-state magnetization acquired with BIRP pulses and FAs of $\alpha = 60^\circ$, and $\beta = 15^\circ$ (14,15). Unfortunately as will be shown, BIR-4 and BIRP pulses at 3T can be limited by their RF power requirements.

The aim of the present work is to develop safe hardware and a protocol for efficient, accurate, cardiac metabolite quantification at 3T using adiabatic pulses. Numerical simulations of the Bloch equations are used to predict the performance of adiabatic BIR4/BIRP excitation pulses in the presence of a non-uniform RF excitation field, B1, and off-resonance B_0 . It is shown that the threshold of B1 above which BIR4 pulses provide a uniform FA is higher for smaller FAs compared to $\text{FA}=90^\circ$. As a consequence, achieving adequate B1 for the desired FA in the heart at 3T, leads to elevated RF power requirements and hence the potential for tissue heating (16). Unfortunately, increasing the pulse duration to reduce the pulse power results in signal losses that depend on the metabolite transverse relaxation times (T2) as well as the FA, and can introduce errors in dual-angle T1 measurements.

Here, to overcome possible T2 quantification biases, we replace the BIRP pulses in cardiac ^{31}P MRS protocols with 90° adiabatic half passage pulses (AHP) (17), and increase their BW by introducing frequency sweep cycling (FSC). An alternative T1 measurement protocol based on two repetition times (TR) is then introduced, and its accuracy is validated in simulations and phantom studies at 3T. We apply this dual-TR method to measure the ^{31}P T1s of PCr and ATP in normal human calf and cardiac muscle at 3T, using an optimized, heat-tested, dual loop transmit/receive coil. The results are compared to conventional partial saturation (PS) measurements, and the accuracy of the dual-TR method in predicting the fully-relaxed magnetization is determined.

Theory

Numerical simulations

Adiabatic pulses are characterized by their RF waveform with B1 amplitude $|B1^+|$, normalized frequency sweep waveform $f(t)$, and maximum frequency sweep f_{max} . The evolution of the magnetization vector is numerically simulated in *Matlab* (*Mathworks*, Natick, MA, USA) using the Bloch equations to describe both rotation and relaxation during tanh/tan-modulated AHP and BIR4 pulses (18), digitized at 5 μs intervals.

|B1⁺| threshold for BIR4 pulses

The accuracy of quantitative ³¹P MRS studies employing BIR4 pulses and T1 measurements by the dual angle method depends critically on the fidelity of the applied FA. We define the B1-threshold as the value of |B1⁺| above which the error in the transverse magnetization, M_{xy} after excitation, is ≤ 5%. This magnetization error (%) is given by $(M_{xy} - M_0 \sin(\theta)) / M_0 \sin(\theta) \times 100$, where θ is the nominal FA. Contours of the magnetization errors for BIR4 pulses of duration $\tau = 5\text{ms}$, with $f_{\text{max}} = 10\text{kHz}$ and $\theta = 15^\circ$ and 90° computed with no relaxation effects as a function of the off-resonance frequency, $\Delta\Omega$, and |B1⁺|, are shown in Fig. 1. The 5% threshold for a BW of $\pm 100\text{Hz}$ increases from $25\mu\text{T}$ to $45\mu\text{T}$ as the FA is reduced from 90° to 15° (Fig. 1a, Fig. 1b). Thus, the minimum |B1⁺| required to achieve the threshold is determined, in part, by the lowest FA used.

The peak |B1⁺| threshold can be reduced by increasing the pulse duration. Fig. 1c shows that the |B1⁺| threshold for the 15° FA is reduced to $22\mu\text{T}$ when τ is increased from 5ms to 15ms and $f_{\text{max}} = 6\text{kHz}$. Thus, in the absence of relaxation effects, one might conclude that use of long pulses will suffice to provide accurate FAs and T1 estimates at lower |B1⁺| levels. This will also reduce RF power deposition.

Excitation pulses with relaxation effects

During the application of a B1 directed along the x-axis in the presence of relaxation and off-resonance effects resulting from either field inhomogeneity or chemical shift, the Bloch equation in the rotating frame can be expressed as (19,20):

$$\begin{aligned} \frac{dM_x}{dt} &= -\frac{M_x}{T_2} + \Delta\omega(t) M_y, \\ \frac{dM_y}{dt} &= -\frac{M_y}{T_2} - \Delta\omega(t) M_x + \gamma |B_1^+| M_z, \\ \frac{dM_z}{dt} &= -\gamma |B_1^+| M_y + \frac{M_0 - M_z}{T_1}, \end{aligned} \quad (1)$$

where M_z is the longitudinal magnetization, M_x and M_y are the transverse magnetization components, γ is the gyro-magnetic ratio, and $\Delta\omega(t) = \Delta\Omega + f_{\text{max}}f(t)$. When the pulse duration $\tau \ll T_1$, longitudinal relaxation during the pulse can be neglected. Breaking the pulse into n small FAs of sample duration $t_s = \tau/n$ and neglecting off-resonance effects during t_s , the solution to the Bloch equation is (21):

$$\begin{aligned} \underline{M}(t_s, T_2) &= E(t_s, T_2) R_x(\gamma B_1^+(t_s) t_s) \underline{M}_i, E(t_s, T_2) = \begin{bmatrix} E_2 & 0 & 0 \\ 0 & E_2 & 0 \\ 0 & 0 & 1 \end{bmatrix}, \\ E_2 &= e^{-\frac{t_s}{T_2}}, \underline{M}_i = \begin{bmatrix} 0 \\ 0 \\ M_0 \end{bmatrix} \end{aligned} \quad (2)$$

where R_x is a rotation matrix about the x-axis. For a long pulse with |B1⁺| almost constant during τ as the BIR4 and AHP pulses are, the general solution becomes:

$$\underline{M}(\tau, T_2) = \left[E(t_s, T_2) R_x(\gamma B_1^+((n-1)t_s) t_s) \dots E(t_s, T_2) R_x(\gamma B_1^+(t_s) t_s) E(t_s, T_2) R_x(\gamma B_1^+(0) t_s) \right] \underline{M}_i \quad (3)$$

For a long pulse, T2 affects M_z , M_x and M_y as a result of the interchange of the decay and rotation matrices. In fact for a continuous constant |B1⁺| analogous to a continuous saturation pulse with $\gamma|B_1^+| \gg 1/(2.T_2)$ the closed-form solution is (19):

$$\begin{aligned} M_{xy} &= ie^{\frac{\tau}{T_2}} \sin(\gamma |B_1^+| \tau) M_0, \quad M_{xy} = M_x + iM_y \\ M_z &= e^{\frac{\tau}{T_2}} \cos(\gamma |B_1^+| \tau) M_0 \end{aligned} \quad (4)$$

Because an analytic solution of the Bloch equations including T2 relaxation is not available for this type of amplitude and frequency modulated adiabatic pulse, the magnetization is evaluated numerically from Eq. [3], by applying rotations along

$B_{eff}(nt_s) = B_1(nt_s) \bar{x} + \Delta\omega(nt_s) \bar{z}$ in the doubly-rotating frame (21). The resultant magnetization at the end of a 15ms BIR4 pulse with $f_{max} = 6\text{kHz}$, $|B_1^+| = 100\mu\text{T}$ and $T_1/T_2 = 6\text{s}/50\text{ms}$, is shown as a function of FA in Fig. 1d. Both M_z and M_{xy} at the end of the pulse are attenuated to 83% relative to the magnetization in the absence of T2 decay. A similar effect has been reported with frequency selective adiabatic inversion pulses, used to suppress long-T2 components in ultra-short T2 imaging (22,23).

The attenuation effect can be represented by attenuation factors $E_p^z \leq 1$ for M_z and $E_p^{xy} \leq 1$ for M_{xy} , which are functions of $\tau, f_{max}, |B_1^+|$ and T2. Assuming only a longitudinal magnetization (M_z^-) at the start of the pulse, the magnetization at the end of the pulse is:

$M_z^+ = E_p^z \cos(\theta) M_z^-$ and $|M_{xy}| = E_p^{xy} \sin(\theta) M_z^-$. The steady-state partially-saturated net magnetization after the $(n+1)^{\text{th}}$ pulse with $M_z^-(n+1) = M_z^-(n)$ is:

$$\begin{aligned} M_z^- &= M_0 (1 - E_1) + E_1 E_p^z M_z^- \cos \theta, \quad E_1 = e^{-\frac{TR}{T_1}} \\ |M_{xy}(\theta)| &= M_0 \left(\frac{(1-E_1)}{(1-E_p^z E_1 \cos \theta)} \sin \theta \right) E_p^{xy} \end{aligned} \quad (5)$$

Importantly, Eq. [5] deviates from that used to determine T1 in the dual-angle method when $E_p^z \neq E_p^{xy} \neq 1$ (15). Eq. [5] shows that the T2 attenuation factor E_p^{xy} causes only a decrease in the SNR of the received signal, independent of FA. However, the E_p^z term in the denominator *does* scale with FA and E1. Thus, T1-corrections applied to partially-saturated signals acquired with long adiabatic pulses such that $E_p^z \neq 1$, can potentially result in FA-dependent errors in computing the fully-relaxed signal for metabolite quantification if E_p^z is ignored.

The T2 attenuation of the steady-state magnetization following the 50th pulse computed from the Bloch equations is shown in Fig. 2, as a function of FA for a 10ms, 10kHz BIR4 pulse, in a sample with $T_1/T_2=6\text{s}/50\text{ms}$, and $TR=1\text{s}$, as compared with $TR=50\text{s}$. At $TR=1\text{s}$, the effect of E_p^z in Eq. [5] reduces $|M_{xy}|$ from 90% of the value of $[M_0 \sin \theta]$ at $FA = \pm 90^\circ$ to about 60% of its value at $FA = \pm 20^\circ$ (Fig. 2a). Note that the denominator in Eq. [5] approaches unity for $FA = 90^\circ$ independent of TR, whereupon the attenuation factor is equivalent to its fully-relaxed value (at $TR=50\text{s}$). Because the error in the magnetization excited by long pulses increases as FA decreases, the steady-state signals acquired with the two FAs of the dual angle or any variable flip-angle method of measuring T1 are altered differentially.

Effect of T2 on dual angle T1 measurements with long BIR4 pulses

The dual-angle T1 is a function of the two FAs, α and β with $180^\circ \geq \alpha > \beta \geq 0^\circ$ (15):

$$T1 = -TR/\ln[q], \text{ where } q = \frac{\sin(\alpha) - R \sin(\beta)}{\cos(\beta) \sin(\alpha) - R \cos(\alpha) \sin(\beta)}, \quad (6)$$

where R is the ratio of the two steady-state signals acquired with the two FAs. From Eq. [5] we see that the E_p^{xy} factor cancels out when computing R , but the effect of the E_p^z term does not. The signal ratios with (R_a) and without (R) T2 attenuation accounted for are:

$$R = \frac{(1 - E_1 \cos \beta) \sin \alpha}{(1 - E_1 \cos \alpha) \sin \beta}, \text{ and } R_a = \frac{(1 - E_p^z E_1 \cos \beta) \sin \alpha}{(1 - E_p^z E_1 \cos \alpha) \sin \beta} \quad (7)$$

Because $\cos \alpha < \cos \beta$, $0 < E_p^z \leq 1$ and $(1 - E_p^z) E_1 \cos \beta \geq (1 - E_p^z) E_1 \cos \alpha$ then, $(-E_1 \cos \alpha - E_p^z E_1 \cos \beta) \geq (-\cos \beta - E_p^z E_1 \cos \alpha)$. By adding the positive term $(1 + E_1 E_p^z \cos \alpha \cos \beta)$ to both sides of the inequality, we obtain,

$$(1 - E_p^z E_1 \cos \beta)(1 - E_1 \cos \alpha) \geq (1 - E_p^z E_1 \cos \alpha)(1 - E_1 \cos \beta) \quad (8)$$

Eqs. [7] and inequality [8] lead directly to the condition, $R_a \geq R$. Because $\alpha > \beta$, and $\sin \alpha \sin \beta (\cos \beta - \cos \alpha) R_a \geq \sin \alpha \sin \beta (\cos \beta - \cos \alpha) R$.

$$\therefore q = \frac{\sin(\alpha) - R \sin(\beta)}{\cos(\beta) \sin(\alpha) - R \cos(\alpha) \sin(\beta)} \geq q_a = \frac{\sin(\alpha) - R_a \sin(\beta)}{\cos(\beta) \sin(\alpha) - R_a \cos(\alpha) \sin(\beta)} \quad (9)$$

Thus, in the presence of T2 relaxation during BIR4 pulses, use of Eq. [6] and R_a , can introduce errors such that the observed T1 $\leq$ the true T1.

It can be seen from Eqs. [6] and [7] that T1 errors are a function of both T2 as well as T1/TR. Fig. 3 is a numerical simulation of two dual angle protocols for estimating the T1 as a function of T2 and T1/TR operating at 75 μ T. Above the B1 threshold T1 underestimation errors increase as T1/TR and/or T2 decreases, with the larger errors arising from the longer (15ms) pulse, shorter T2s, and longer T1s. Published ^{31}P metabolite T2s for PCr of 330 ± 30 ms and 78 ± 13 ms for γ -ATP in skeletal muscle at 3T (24) are not independently confirmed but ATP T2s of around 60ms are reported at 1.5T (25). If correct, these T2s should be sufficiently long to avoid significant T1 errors with BIR4/BIRP pulses of $\tau \leq 5$ ms with adequate $|B1^+|$ threshold, as deployed previously (14,15,26), but not for longer pulses (Fig. 3). These results reflect the problems of the power requirements of low-angle adiabatic pulses, the need for accurate FAs in quantitative work, and the pitfalls of increasing τ to compensate for inadequate $|B1^+|$ when pulse power is limited, to which MRS at higher B_0 -fields is prone.

T1 measurement using Dual TR

The main problem with Eq. [5] is the $E_p^z \cos \theta$ term in the denominator, which increases at low FA as noted. A solution that eliminates the T2 errors for long adiabatic pulses by fixing FA=90°, requires varying the TR. The minimum number of TR values is two, whence, the *dual TR* (2TR) method. By analogy to the dual angle method, the ratio of magnetization acquired at the two TRs is:

$$R_{2TR} = \frac{(1 - E_1^s) E_p^{xy}}{(1 - E_1^f) E_p^{xy}} = \frac{(1 - E_1^s)}{(1 - E_1^f)}, \text{ where } E_1^s = e^{-\frac{TR_2}{T_1}} \text{ and } E_1^f = e^{-\frac{TR_1}{T_1}}. \quad (10)$$

The remaining E_p^{xy} term just attenuates the transverse magnetization and reduces the effective SNR. Because an analytic solution to Eq. [10] is limited to certain TRs (27), a lookup table for T1 was created from Eq. [10] at a resolution of 0.01s, for the two TRs used for the measurement.

Anticipated ^{31}P MRS T1 values of the PCr and γ -ATP in muscle and heart all fall in the range 1-7s (15,24). Monte-Carlo simulations are used to compare the SNR performance of the 2TR versus the dual-angle method (neglecting the T2/long pulse effects) over that range, and to select the best combination of TR and number-of-averages (NA). The ratio is modeled as:

$$R_{MC} = \frac{|M_{xy}(\alpha, TR_2, T1)| + \text{noise}_2}{|M_{xy}(\beta, TR_1, T1)| + \text{noise}_1}, \text{ with noise}_1 = \text{Gaussian noise}, \sigma_{\text{noise}} = \sigma / \sqrt{NA \times N_{\text{slice}}} \quad (11)$$

with $\alpha \neq \beta$, $TR_2 = TR_1$ for the dual-angle method experiment, and $\alpha = \beta = 90^\circ$, $TR_2 \neq TR_1$ for the 2TR experiment. A receiver noise variance (σ) of $0.16M_0$ is assumed, corresponding to an SNR~6 per fully-relaxed excitation, and the total noise variance (σ_{noise}) for each measurement was scaled by NA and the number of slices ($N_{\text{slice}} = 32$), as in a typical one-dimensional chemical shift imaging experiment (1DCSI) (28). For each T1 value, Gaussian noise was added 5000 times to calculate the SD of the T1 measurement. The total acquisition time for each T1 experiment, $(NA_1 \times TR_1 + NA_2 \times TR_2)N_{\text{slice}}$, was kept constant at 20 ± 1 min. Different TR combinations were studied and the ones yielding the lowest % errors for the expected T1 range for PCr and γ ATP in the heart are plotted in Fig. 4. This shows that the 2TR method can be performed with T1 errors $\leq 10\%$, and is comparable to the dual-angle method (14) over the range of T1 likely observed in the human heart.

As the SNR analysis is unaffected by pulse type, the 90° BIR4 pulses for the 2TR method are replaced by AHP pulses to reduce $|B1^+|$ requirements. The % transverse magnetization errors, for $FA = 90^\circ$, and the % longitudinal residual magnetization ($|M_z|/M_0 \times 100$) on-resonance for 10ms AHP pulses, are computed as a function of $|B1^+|$ and T2. The $|B1^+|$ threshold, defined by the 5% error contour to ensure that Eq. [10] is correct and to eliminate the E_p^z term in Eq. [5], is found to be $\sim 13\mu\text{T}$ for the 10ms pulse (compared to $\sim 20\mu\text{T}$ for BIR4 pulses).

A steady-state simulation of the 2TR method using the 10ms AHP pulses for an extreme case of a sample containing two moieties with T1s of 2s and 6s, and $T2 = 50\text{ms}$, reveals that the errors in T1 are $\leq 5\%$ for $|B1^+| \geq 15\mu\text{T}$ on-resonance (Figs. 5a, c). However the BW of the $15\mu\text{T}$ AHP pulse is insufficient to excite two moieties such as PCr and γ ATP separated by $\sim 130\text{Hz}$ at 3T, even when the RF pulse frequency is centered between them. Recognizing that the AHP excitation response is asymmetric, we alleviate the problem by alternately cycling the sign of the frequency sweep of the AHP. Repeating the simulation with this frequency-sweep cycling (FSC) yields a BW of 200Hz for $|B1^+| > 20\mu\text{T}$, with T1 errors $\leq 10\%$ (Figs. 5.b, 5.d). Fig. 5 shows that with T2 of 50 ms the BW over which T1 can be measured accurately is increased for shorter T1s.

Methods

Hardware

A transmit coil for 3T ^{31}P MRS is designed to achieve a $|\text{B1}^+|$ of $\sim 20\mu\text{T}$ over an $8\times 8\text{ cm}^2$ area at a depth of $\sim 10\text{cm}$ in the body, while not exceeding the local specific absorption rate (SAR) guideline of 10W/kg averaged over 10g of tissue (29). The peak root-mean-square (rms) power at the broadband amplifier was 4kW during the pulse, but 30% is lost in transit to the coil, leaving $P_{\text{peak}} = 2.8\text{kW}$ of available power. Local SAR is computed from a chest model consisting of an 8mm fat layer with dielectric constant $\epsilon = 7$ and conductivity $\sigma_c = 0.04\text{S/m}$, over a semi-infinite muscle layer with $\epsilon = 76$, $\sigma_c = 0.68\text{S/m}$ (30), using the electromagnetic (EM) method-of-moments (MoM), with *FEKO Inc* (Stellenbosch, South Africa) software. Single and double loop transmit coils wound from flat 1-cm conductors and tuned to 51.7 MHz with distributed capacitors are modeled with a gap between the coils and the body iteratively adjusted to limit the local SAR, which is highest near the windings.

The current flowing in the coil at peak applied power is $I = \sqrt{2 \times P_{\text{peak}} / (R_b + R_c)} \approx 21\text{A}$ assuming coil losses $R_c = 0.1R_b$, where R_b is the calculated body load resistance (16).

The analysis shows that a double loop coil with loop diameters of 17cm and 11cm gives the desired $|\text{B1}^+|$ for the 10ms FSC AHP at depth 10cm in the body with the coil conductors 18mm away from the body surface (Fig. 6). The maximum local SAR averaged over 10g of tissue is calculated using the simulated electric fields $\mathbf{E}$ where (16):

$$\text{SAR} = \int_{\text{volume}} \frac{\sigma_c |\mathbf{E}(r)|^2}{2\rho} dr \times \frac{\text{Pulse Duration}}{TR}, \text{ where } \rho = 1000\text{kg/m}^3 \quad (12)$$

This results in a maximum local SAR $\leq 10\text{W/kg}$ at the feed point with $TR \geq 1.2\text{s}$ at P_{peak} using the 10ms pulse. The coil is pictured in Fig. 6b: a separate 8-cm diameter coil is deployed for reception (28). The ratio of unloaded-to-loaded transmit coil quality factors (Q) is 9, confirming the $R_c = 0.1R_b$ assumption above. A coil interface with a 48dB gain, 0.5dB noise figure (NF) preamplifier, coil identification circuitry, and current drivers is built to connect the coils to the scanner. The NF of the entire receiver chain measured by the cold 50Ω -resistor method is 0.9dB (31). Because the computed transmit field showed a lateral shift in the maximum field by $\sim 3\text{cm}$ from the coil center (Fig. 6a,b), the receiver coil is shifted off-axis by 3cm, and 18mm above the transmitter in a plastic housing. A vitamin-D pill (Rocaltrol Calcitriol) is placed in the center to facilitate localization on ^1H MRI.

B1 performance and safety tests

On-axis $|\text{B1}^+|$ field strength and heat-testing of the coil-set are performed on a $33\text{cm} \times 33\text{cm} \times 20\text{cm}$ deep polyacrylamide gel phantom containing 3.5g/l NaCl with measured $\epsilon = 80$, $\sigma_c = 0.65\text{S/m}$, to mimic chest loading conditions (16). A phantom tube filled with 300 mM inorganic phosphate (Pi) is placed in a 2-cm cylindrical hole in the center of the phantom, above the coils. Localized second-order shimming is based on acquired B_0 -maps using ^1H MRI (32). ^{31}P 1DCSI with slice thickness $ST = 5\text{mm}$ is applied with square excitation pulses to measure $|\text{B1}^+|$ from the location of the signal nulls that correspond to 180° pulses.

The temperature is measured at four locations in the phantom close to the coil using a 4-channel fiber optic temperature system (*Neoptix, Inc.*). SAR is calculated from the derivative of the temperature rise, ΔT ; (16,33):

$$SAR = \frac{d\Delta T}{dt} C, \quad (13)$$

where $C = 4180 \text{ J / kg}^\circ\text{C}$ is the heat capacity of water. This experiment is conducted with the 10ms AHP pulses at $TR = 750\text{ms}$ for 6min.

Phantom T1 experiments

The scanner is programmed with BIR4 and the new FSC AHP pulses. Phantom experiments are performed to validate the 2TR method (with $TR = 2, 12\text{s}$) against the IR method, and to test its performance as a function of depth from the coil. The T1s of seven 15-cm long tubes of Pi doped with NiCl_2 (0-58 μMol) (34,35) are first determined using an eleven point-inversion recovery (IR) measurement performed with FSC AHP pulses ($\tau = 10\text{ms}$, $f_{\text{max}} = 6\text{kHz}$, $NA = 2$, $TR = 40\text{s}$). The spectra are analyzed using AMARES / MRUI software (36) and T1 values obtained with a three-parameter exponential fit.

The 10ms, 6kHz sweep FSC AHP excitation pulses are then applied on-resonance in both non-localized and 1-cm resolution 1DCSI 2TR T1 measurements of each tube, with TRs of 2s ($NA = 6$) and 12s ($NA = 2$). These experiments are repeated at -70Hz , -140Hz and 70Hz off-resonance to examine BW limitations with depth.

In vivo experiments

All human studies are approved by the Johns Hopkins Institutional Review Board with subjects providing written, informed consent. ^{31}P MRS metabolite T1 measurements in the calf muscle of 9 healthy volunteers (age = 35 ± 9 yrs, 6 men and 3 women) are conducted with subjects lying supine on the coil. The calf is shimmed to $\sim 20\text{Hz}$ ^1H line-width using MRI-guided 2nd-order shimming. The ^{31}P MRS frequency is centered between the PCr and γ -ATP resonances, and an un-localized progressive saturation (PS) experiment performed with $TR = 1.3, 2, 3, 4, 6, 8, 12, 16, 25, 30$ and 40s ($NA = 24, 6, 6, 6, 4, 4, 2, 2, 2, 2$) using 6 kHz sweep 10 ms FSC AHP excitation pulses. Three 1-cm resolution 1DCSI experiments are performed at $TR = 2\text{s}$ ($NA = 6$), 4s ($NA = 4$) and 12s ($NA = 2$). Total scan time is ≤ 90 min.

The 11-point unlocalized calf measurements are fitted to a two-parameter curve $S(TR) = M_0(1 - E1)$ to obtain T1. The 2TR method is then applied to a subset of the same data to estimate T1s using one short TR value (2, or 4s) and a long TR (12s). Because the T1s are in practice used for quantification to estimate the fully-relaxed M_0 from data acquired at much shorter TRs (26), estimates of M_0 obtained from each TR combination are compared to the $TR = 40\text{s}$ measurement to obtain the error in predicting M_0 . For the 1DCSI experiments, metabolite T1s in the six slices closest to the coil are averaged for comparison with non-localized values.

^{31}P MRS heart studies are next performed on 10 healthy volunteers (age = 33 ± 7 yrs, 7 men and 3 women) to test whether conventional dual angle T1 measurements could be used to measure cardiac metabolite T1s with the above coil set-up, available power and the shorter BIR4/BIRP pulses ($\tau = 5\text{ms}$, $f_{\text{max}} = 10\text{kHz}$). The BIR4 B1-threshold is $42 \mu\text{T}$, limiting efficacy to a depth of $\sim 6\text{cm}$ from the coil at P_{peak} (Fig. 6). Subjects are positioned prone with the heart above the ^{31}P coil and ECG electrodes attached to the back. ^1H MRI-guided second-order shimming is performed as above. Two cardiac-gated 1DCSI data sets are acquired at $TR \sim 1\text{s}$ (one cardiac cycle) with $FA = 60^\circ$ and 15° ($NA = 12$ and 24 ; 32 1-cm slices); total scan time $\sim 30\text{min}$. T1 is calculated from the dual-angle method Eq. [6] (15).

Finally, cardiac 2TR and PS ^{31}P MRS studies employing the 10ms FSC AHP pulses are performed separately in 10 further volunteers (age = 34 ± 7 yrs, 6 men and 4 women). In these studies, four cardiac-gated 1DCSI data sets are acquired at TR $\approx 2, 4, 12$, and 32s (NA = 24, 12, 4, and 2; BW = 2.5kHz; 16 1-cm slices). T1 is analyzed the same way as for the leg PS and 2TR data, and the results are compared. Total scan time is ≤ 60 min.

Results

Safety testing

On-axis measurements of $|B_1^+|$ field strength agree with the computed values, as shown in Fig. 6c. The maximum measured SAR occurred at the transmit coil input and was 15W/kg for the 10ms AHP pulse applied at TR=750 ms, equivalent to 9.4 W/kg for TR =1.2s. This agrees with the computed maximum local SAR of 8.8 and 10W/kg for the 10g and 1g averages, respectively.

Phantom experiments

Results from experiments to validate the 2TR method on 7 different Pi samples are plotted in Fig. 7. Fig. 7a shows that the non-localized on-resonance 2TR method accurately predicts the IR T1 values with an average SD of 3%. The 1DCSI data plotted in Fig. 7b show that measurements are good to 10-11cm from the coil housing, again within a 3% SD. The ten-slice average 1DCSI measurements are also included in Fig. 7a. The T2 of the 8.3 μmol doped phantom in Fig. 7 was ~ 50 ms. At the higher NiCl_2 levels used in Fig. 7, the T2 of Pi is slightly shortened thereby providing a test of the 2TR method under conditions of $T_2 \leq 50$ ms.

The off-resonance performance of the 2TR method in both unlocalized and 10-slice averaged 1DCSI measurements is reported in Table 1. T1 measurements on-resonance agree with those at ± 70 Hz. However, the errors as indexed by the SD, increase after slice 9 at ± 70 Hz, two slices shallower than on-resonance. At -140 Hz the mean T1 measurement is 10% higher than on-resonance.

In vivo experiments

Exemplary calf muscle ^{31}P 1DCI spectra and a corresponding image are shown in Fig. 8. The experimental PS and 2TR T1 values for PCr and γATP are listed in Table 2. The 2TR T1 values averaged over six 1DCSI slices (Fig. 8b) agree with the non-localized results (Table 2). The % error in predicting M_0 based on a T1 estimate made using two different TR combinations, and applying it to the signal measured at the shorter TR, is reported (Table 2). The M_0 of calf muscle PCr and $\gamma\text{-ATP}$ at TR =40s is predicted with an accuracy of 7% or better using TR1 =2s or 4s and TR2 =12s (Table 2).

Anterior myocardial ^{31}P 1DCI spectra exhibited an average SNR of ~ 50 for PCr in all volunteers, at a depth of 7-8cm from the surface (Fig. 8c,d). The results for T1 (Table 2) show that 2TR measurements acquired with 10 ms AHP pulses at both 2/12s and 4/12s TRs agree with four-point PS measurements within 10%. The error in predicting M_0 at TR =32s based on the 2TR T1 applied to measurements at TR =2 or 4 s is also $<10\%$. The dual angle method with 5ms BIR4/BIRP pulses yielded the same mean metabolite T1 values as both the 2TR and the PS methods. However, the uncertainty, as indexed by the SDs, is several times higher, reflecting marginal operation of the BIR4/BIRP pulses at the heart.

Discussion

We have shown that bandwidth and RF power limitations at 3T may necessitate significant modifications to the quantitative surface coil ^{31}P MRS protocols previously used at 1.5T, where use of 1-5ms adiabatic pulses such as BIR4 or BIRP provided uniform excitation (14,15,26). The correction of signals for partial saturation effects requires precise knowledge of FAs and metabolite T1s, and both are central to determining absolute metabolite concentrations in patient cardiac studies. With even a modestly sized dual 17/11-cm transmit coil connected to a 4kW power amplifier at 3T, $|B_1^+|$ is limited to $\sim 20\mu\text{T}$ at cardiac depths of 9-10cm from the coil's housing. As a consequence, without significantly increasing the RF driving power, the BIR4 pulse-length must be increased to achieve the $|B_1^+|$ threshold for uniform FA at these depths, especially when low FAs are called for. Numerical Bloch equation simulations show that T2 decay can attenuate the longitudinal magnetization during long BIR4 pulses in a manner that varies with FA and T2 (Fig. 2). In the absence of accurate knowledge of T2, this can introduce errors and uncertainty in the T1 measured by the dual-angle method especially when $\tau \geq 10$ ms, in addition to errors in the correction of signals acquired at different BIR4 FAs.

Recognizing that such affects are ameliorated at high FAs, we introduced the 2TR method of measuring T1 using two different TRs and 90° AHP pulses whose BW is increased by frequency-sweep-cycling (Fig. 5). With this method, T1 is determined from the ratio of the measured signals with a look-up table, and the errors in T1 due to T2 decay are eliminated, as shown by Bloch equation simulations. Monte-Carlo simulations are used to optimize the choice of TRs for the ^{31}P MRS range $1 \leq T1 \leq 7$ s, consistent with *in vivo* studies. This analysis shows the sensitivity of T1 measurements to be comparable to the dual-angle method (Fig. 4) (14,15,26).

The 3T dual ^{31}P MRS 17/11-cm loop transmit and 8-cm diameter receiver coil set provide a measured $|B_1^+|$ that agrees with computed values (Fig. 6c). Calorimetric and EM MoM calculations of SAR are also in agreement, with local SAR $< 10\text{W/kg}$ (at $\tau=10\text{ms}$) requiring a TR ≥ 1.2 s to remain within the 10-g average safety guidelines for the body (29). In the heart, optimized sequences are run at TR ≥ 2 s, providing an extra safety factor for local SAR. Nevertheless, the local SAR is surprisingly high for such long TRs, and limits the scope for improving performance with shorter adiabatic pulses at higher RF power levels that could increase the penetration depth and reduce T2 effects. In this respect, the longer TRs afforded by the 2TR method provide an added advantage of reducing SAR as compared to the short-TR, dual angle approach.

The experimental set-up provides direct ^{31}P MRS validation of the 2TR method of measuring T1 on different NiCl_2 -doped Pi solutions up to a depth of $\sim 9\text{cm}$, showing agreement to within 3% of values obtained by IR (Fig. 7, Table 1). Applying the 2TR protocol *in-vivo* provides ^{31}P T1 values of PCr and γ -ATP at 3T for skeletal muscle in normal volunteers. The 2TR T1 values agree with the PS measurements to within about 10% with an accuracy that improves with the longer TRs of 4/12s, which are better matched to T1 values, consistent with Fig. 4. The PS T1 values obtained are comparable with recent values of 6.4 ± 0.2 s for PCr and 4.5 ± 0.3 s for γ -ATP in the human calf muscle obtained at 3T using sinc-pulses and STEAM localization (24). They are also similar to literature average T1 values of 6.52s for PCr and 4.32s for γ -ATP recorded at 1.5T (15). Regardless of the apparent T1, for metabolite quantification it is the fully-relaxed signal M_0 that is important, and applying the measured T1 values to the short-TR signal to calculate M_0 yields a mean estimation error $\leq 7\%$.

The T1s of cardiac metabolites measured by the 2TR method with FSC AHP pulses agree with the 4-point PS estimates, and predict M_0 at TR = 32s within 10%. Our normal human cardiac ^{31}P MRS PS T1 values of $5.8 \pm 0.5\text{s}$ for PCr and $3.1 \pm 0.6\text{s}$ for γ -ATP are consistent with previously reported PS values of $5.3 \pm 1.6\text{s}$ for PCr and 2.7 ± 0.6 for γ -ATP measured at 4T (37). The T1 of PCr appears a little higher than at 1.5T (14).

That the mean dual angle cardiac ^{31}P MRS T1 values agree with the 2TR and PS values in practice, suggests that the dual angle protocol is not compromised by T2 effects in cardiac ^{31}P MRS performed with 5 ms or shorter BIR4/BIRP pulses which have been used in the past. On the other hand, the higher B1-threshold for the shorter pulses and the power limitations, appear to compromise the precision of dual angle BIR4/BIRP T1 measurements at 3T, as compared to the FA = 90° FSC AHP approaches (Table 2). While the present study involved a group of nonobese volunteers, heart patients often require deeper ^{31}P MRS penetration, whereupon the FSC AHP protocols and 2TR measurements will be advantageous, at least with the present 3T experimental set-up.

In the past we preferred to measure the β -phosphate of ATP rather than γ -phosphate of ATP, in order to quantify cardiac ATP (1-3,9,26). Here, even the increased bandwidth offered by FSC is insufficient to accurately excite both the PCr and β -ATP peaks at a 9-10 cm target depth with T1 errors < 5%. Reducing the target depth to 5cm under the same operating conditions with the frequency centered at -8.2ppm would overcome this problem. Even so, the measurement of the γ -phosphate of ATP has long been used in human cardiac studies reporting both PCr/ATP ratios and ATP concentrations (38,39). Thus use of γ -ATP instead of β -ATP for quantifying ATP does not represent a significant departure from published approaches (37-39). On the other hand, inorganic phosphate (Pi) at 5ppm, as well as PCr and γ -ATP should be quantifiable with <5% T1 error at depths of up to 6.5cm by setting the transmit frequency at the mid-point, 1.2ppm, assuming that T1/T2 is 5s/50ms for Pi. However, quantitative measures of Pi in human heart have not proven routinely reliable to date, due to its overlap with blood 2,3-diphosphoglycerate (DPG) peaks and/or phosphoester peaks, in addition to its low intrinsic concentration, as is evident in the 4-6ppm region of Fig 8d. For example, de Roos et al were able to quantify cardiac Pi in only 50% of 26 subjects that they studied by proton-decoupled ^{31}P MRS (40). When Pi *can* be resolved, measurement of pH, which depends only on the chemical shift, would not be impaired.

Unfortunately, the longer TRs of the AHP approaches provide little scope for scan-time reductions at 3T, as compared to 1.5T BIR4/BIRP protocols and dual angle measurements. Indeed, the longer TRs for the 2TR method as well as SAR may be factors limiting minimum scan-times for MRS localization sequences that require large numbers of phase-encoding steps, for example. Nevertheless, with the caveat that the new 3T 2TR experiments and the former 1.5T dual angle studies use non-comparable scan parameters (FA, TR, NA, coils), the SNR of the 3T TR = 2s acquisitions is about 1.5-fold higher than that seen in 1.5T TR = 1s FA = 60° acquisitions, for 1-cm 1DCSI cardiac spectra acquired in the same time at each field (n=10 data sets). It should also be feasible to extend the 2TR method to the measurement of CK flux in a similar manner to the adaptation of the dual angle method to four angle saturation transfer (FAST) (26), and we are currently validating such an approach for human cardiac studies.

In conclusion this work addresses some key issues affecting MRS quantification at 3T that are likely to be prevalent at higher fields in general. Practical solutions are provided to solve problems of bandwidth, SAR, and errors associated with the use of adiabatic pulses for uniform excitation. Validated human ^{31}P metabolite T1s are reported for skeletal and heart muscle at 3T.

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Appendix A

List of abbreviations

1DCSI	One dimensional chemical shift imaging
2TR	Dual repetition time
³¹P	Phosphorus
AHP	Adiabatic half passage
ATP	Adenosine tri-phosphate
BIR4	B ₁ independent rotation (4-segments)
BIRP	BIR phase-cycled
B1⁺	RF excitation magnetic field
B₀	Static magnetic field
CK	Creatine-kinase
EM	Electromagnetic
FA	Flip angle
FSC	Frequency sweep cycling
M₀	Fully-relaxed magnetization
MoM	Method of Moments
MRS	Magnetic Resonance Spectroscopy
NA	Number of averages
N_{slice}	Number of slices
NF	Noise figure
PCr	Phosphocreatine
P_i	Inorganic phosphate
PS	Partial saturation
Q	Quality factor
RF	Radio frequency
rms	Root mean square
SAR	Specific absorption rate
SD	Standard deviation
SNR	Signal to noise ratio
T	Tesla

T1	Spin-lattice relaxation time
T2	Transverse relaxation time
TR	Repetition time

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FIG. 1.

Computed (%) error maps for the transverse magnetization, M_{xy} , for BIR4 pulses ($\tau = 5$ ms, $f_{max} = 10$ kHz) under fully-relaxed conditions with infinite T_2 for (a) FA = 90°, and (b) FA = 15°. The B1-threshold is higher at 45 μ T for FA = 15° vs 25 μ T for FA = 90°. (c) Increasing the pulse to $\tau = 15$ ms ($f_{max} = 6$ kHz) reduces the B1-threshold to ~22 μ T for FA = 15°. (d) Longitudinal magnetization M_z (gray), and M_{xy} , (black) calculated with $T_2 = 50$ ms and a single 15 ms BIR4 excitation pulse (solid line) as a function of FA. For comparison, the magnetization for $T_2 = \infty$ is depicted with dashed lines. The attenuation curve and crosses (top) is the ratio of the solid to the dashed curves, $E_p^z = E_p^{xy} = 0.83$ for both M_{xy} and M_z in the absence of partial saturation effects.

FIG. 2.

(a) Computed fractional signal loss for TR=50s (squares) and TR =1s (circles) steady-state (50 excitations); and (b) M_{xy} for a sample with $T_1 = 6s$ and $T_2 = 50ms$ (solid curve) or $T_2 = \infty$ (dashed line) for $-90^\circ \leq FA \leq 90^\circ$. In (b) the difference between the solid and dashed lines shows a significant T_2 effect for a 10ms, 10kHz BIR4 pulse on resonance at $|B_1|$ of $100\mu T$. As seen in (a), at TR = 50s, T_2 attenuates M_{xy} by a constant amount independent of FA, whereas at TR =1s the attenuation is FA-dependent.

FIG. 3.

The %T1 underestimation errors computed for two dual FA experiments as a function of T2 and T1/TR. Simulations are performed for 10kHz BIRP pulses on-resonance with $B_1=75\mu\text{T}$ for pulse durations (a) $\tau=5\text{ms}$, B1-threshold $\sim 43\mu\text{T}$; and (b) $\tau=15\text{ms}$, B1-threshold $\sim 22\mu\text{T}$.

FIG. 4.

(a) T1 look-up curve for obtaining T1 from the ratio of signals from a 2TR experiment with $TR_1 = 2s$, $TR_2 = 12s$. The distribution of the signal ratios in the Monte-Carlo simulations of the effect of low SNR for $T1 = 5$ are shown as gray dashed lines giving rise to corresponding scatter in the T1 measurements. (b) Monte-Carlo simulations of the % error in T1, as indexed by the SD, as a function of T1 for the dual flip-angle experiment at $TR = 1s$ (dashed curves), and the 2TR experiment at $TR = 1$ and $11s$ (blue curve), and $TR = 2$ and $12s$ (black curve). Experiments are simulated with equivalent total scan times of $\sim 20min$, with no T2 effects.

FIG. 5.

T1 error (% , contours) for a 2TR (2/12s) experiment using AHP pulses as a function of off-resonance frequency and B1 amplitude for samples with $T_2 = 50\text{ms}$, and $T_1 = 6\text{s}$ (a, b) and $T_1 = 2\text{s}$ (c, d). Conventional AHP pulses have a limited BW (a, c), especially for the longer T_1 samples. The BW is increased to $>160\text{Hz}$ (b) and $>400\text{Hz}$ (d) for the shorter T_1 by alternating the sign of the frequency sweep for a B1-threshold of $\sim 20\mu\text{T}$ and a T1 error $\sim 10\%$.

FIG. 6.

(a) Computed $|B_1^+|$ -field of the dual loop transmit coil with loop diameters of 17cm and 11cm positioned 18 mm from the body surface for the saline test gel phantom (3.5 g/l NaCl). The field is asymmetric, with maximum (dashed line) displaced by ~3cm from the center. (b) Picture of the 3T ^{31}P MRS coil set with 17/11cm transmit and 8cm diameter receiver coil offset by 3cm eccentric to accommodate the asymmetric B_1 field profile. (c) Computed (solid line) and measured (star points) $|B_1^+|$ measurements in the gel phantom along the axis of maximum intensity/receiver coil axis, obtained with 4kW transmitter power from a 1cm diameter phosphate tube embedded in the gel phantom.

FIG. 7.

(a) T1 measured by the 2TR experiment as a function of the T1 measured by an 11-point non-localized IR experiment for each phantom (star points are unlocalized data; circular points are averages of the 10 shallowest 1DCSI slices). (b) Measured T1s of 300mM Pi phantoms doped with NiCl₂ concentrations of 0, 8.3, 16.6, 25, 33.2, 41.5, 58μmol (top to bottom) as a function of depth from 1DCSI 2TR (2/12s) experiments. Depth performance is ~10cm on resonance, as predicted by simulations.

FIG. 8.

(a) Axial image of the calf muscle of a volunteer annotated to show coil location and 1DCSI slices. (b) ^{31}P 1DCSI spectra as a function of depth corresponding to the image in (a) at $\text{TR} = 12\text{s}$. (c) Annotated heart image showing locations of the coil set and the 1DCSI spectra in a cardiac $3\text{T } ^{31}\text{P}$ MRS study. (d) Cardiac spectrum from slice 7 in the heart at $\text{TR} = 12\text{s}$.

Table 1

Off-resonance performance of 2TR (2/12s) T1 measurements using 10ms FSC AHP pulses. BW decreases and T1 errors increase for long T1s.

	0 μ Mol NiCl ₂		58 μ Mol NiCl ₂	
Off resonance	T1 Avg 1DCSI	T1 NL	T1 Avg 1DCSI	T1 NL
0 Hz	5.7 $\pm$ 0.1	5.8	2.3 $\pm$ 0.1	2.40
-70 Hz	5.9 $\pm$ 0.5	5.8	2.30 $\pm$ 0.1	2.23
-140 Hz	6.3 $\pm$ 0.9	6.4	2.3 $\pm$ 0.1	2.29
+70Hz	5.7 $\pm$ 0.5	5.7	2.3 $\pm$ 0.3	2.27
IR NL	5.8		2.30	

Table 2

In vivo 3T T1 values of calf and cardiac muscle metabolites in 9 and 20 healthy volunteers, respectively. Data are acquired by non-localized (NL) PS, by IDC SI (ID) 2TR methods with TR1/TR2 = 2/12s and 4/12s, and by the 1DCSI dual angle method with TR~1s at 3T. “M₀% error” is the error in predicting the fully-relaxed magnetization.

Tissue		Method	PS	2TR ID TR 2/12	2TR ID TR 4/12	2TR NL TR 2/12	2TR NL TR 4/12	Dual angle TR=1
Calf muscle	PCr	T1 [sec]	6.8±0.3	7.7±0.4	7.1±0.5	7.7±0.4	7.1±0.6	
		M ₀ % error	0.9±0.7			7.2±2.0	5.0±2.5	
	γ-ATP	T1 [sec]	5.4±0.6	4.8±0.4	5.1±0.5	4.7±0.3	5.1±0.7	
		M ₀ % error	1.0±0.7			7.0±5.0	5.0±3.3	
Heart muscle	PCr	T1 [sec]	5.8±0.5	5.9±0.8	5.3±0.8			5.7±3.3
		M ₀ % error	2.0±1.0	9.0±3.0	8.0±6.0			
	γ-ATP	T1 [sec]	3.1±0.6	2.8±0.5	2.8±0.7			2.8±2.0
		M ₀ % error	4.0±2.0	9.0±4.0	9.0±4.0			