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Four-Angle Saturation Transfer (FAST) Method for Measuring Creatine Kinase Reaction Rates In Vivo

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Abstract

A new fast method of measuring kinetic reaction rates for two-site chemical exchange is described. The method employs saturation transfer magnetic resonance spectroscopy (MRS) and acquisition of only four spectra under partially saturated, high signal-to-noise ratio (SNR) conditions. In two acquisitions one of the exchanging species is saturated; the other two employ a control saturation. Each pair of acquisitions is applied with two different flip angles, and the equilibrium magnetization, relaxation times, and reaction rates are calculated therefrom. This four-angle saturation transfer (FAST) method is validated theoretically using the Bloch equations modified for two-state chemical exchange. Potential errors in the rate measurements due to the effects of exchange are evaluated for creatine kinase (CK) metabolism modeled for skeletal and heart muscle, and are found to be <5% for forward CK flux rates of $0.05 \leq k_f \leq 1.0 \text{ s}^{-1}$, and up to a 90% depletion of phosphocreatine (PCr). The effect of too much or too little saturating irradiation on FAST appears to be comparable to that of the conventional saturation transfer method, although the relative performance deteriorates when spillover irradiation cuts the PCr signal by 50% or more. “FASTER” and “FASTest” protocols are introduced for dynamic CK studies wherein [PCr] and/or k_f changes. These protocols permit the omission of one or two of the four acquisitions in repeat experiments, and the missing information is recreated from initial data via a new iterative algorithm. The FAST method is validated empirically in phosphorus (³¹P) MRS studies of human calf muscle at 1.5 T. FAST measurements of 10 normal volunteers yielded the same CK reaction rates measured by the conventional method ($0.29 \pm 0.06 \text{ s}^{-1}$) in the same subjects, but an average of seven times faster. Application of the FASTER algorithm to these data correctly restored missing information within seven iterations. Finally, the FAST method was combined with 1D spatially localized ³¹P MRS in a study of six volunteers, yielding the same k_f values independent of depth, in total acquisition times of 17–39 min. These timesaving FAST methods are enabling because they permit localized measurements of metabolic flux, which were previously impractical due to intolerably long scan times.

Keywords

saturation transfer; reaction rates; creatine kinase; high-energy phosphate; energy metabolism

Compromised energy metabolism and energy deprivation appear to play a central role in many disease states, including ischemic heart disease (1), heart failure (2), stroke and congenital myopathies (3). The creatine kinase (CK) reaction is important in cellular energy metabolism,

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reversibly transferring high-energy phosphate between adenosine triphosphate (ATP) and phosphocreatine (PCr):

where k_f and k_r are the pseudo-first-order forward and reverse rate constants. Today, the endogenous, in vivo concentrations of PCr, ATP, and H^+ (pH) can be measured noninvasively in humans at 1.5 T with phosphorus (^{31}P) magnetic resonance spectroscopy (MRS) (4–6), and the total concentration of phosphorylated plus unphosphorylated creatine ($\text{CR} = \text{PCr} + \text{Cr}$) with proton (^1H) MRS of the N-methyl resonance (7–10). If the CK flux and rate constants k could also be measured noninvasively in humans, the chemical function of the CK reaction could be completely characterized, and its role in heart failure and other disease states directly assessed.

In fact, measurements of CK reaction rates have long been possible in cells and isolated perfused animal organs placed in conventional MRS spectrometers using ^{31}P magnetization transfer techniques (11–14), and by using surface MRS detector coils placed on or sutured to the organ of interest in otherwise intact animals (15–17). In the standard experiment, the γ -phosphate resonance of ATP (γ -ATP) is saturated (or inverted) by chemical-selective irradiation. This results in a reduction in the PCr signal to a value M'_0 from its fully-relaxed equilibrium value of M_0 , due to the forward flux of phosphate through the CK reaction and the replenishment of PCr with saturated (or inverted) phosphate via the reverse reaction.

For the standard saturation experiment assuming a two-site exchange model, the fractional reduction in M_0 is equal to k_f in units of the spin-lattice relaxation time T'_1 of PCr measured with the γ -ATP saturated (designated by primes):

$$k_f T'_1 = 1 - M'_0 / M_0. \quad [1]$$

At equilibrium, the reverse rate constant is given by:

$$k_r = k_f M_0 (\text{PCr}) / M_0 (\gamma - \text{ATP}). \quad [2]$$

Thus, the determination of k_f and k_r requires measurements of three parameters: M'_0 , M_0 , and T'_1 .

Unfortunately, because 1) M'_0 and M_0 are defined under fully-relaxed conditions; 2) conventional methods for measuring T_1 require multiple acquisitions, including some under-fully-relaxed conditions; and 3) the metabolite ^{31}P T_1 's are characteristically long (~2–7 s (18)), the standard magnetization transfer experiment is very inefficient in delivering signal-to-noise ratio (SNR) per unit time. This severely limits its utility for spatially localized MRS experiments, rendering it all but impractical for human applications. Indeed, few localized (19–23) and fewer human (22–24) studies have been reported, and the problem of accommodating (in a tolerable MRS exam time) the relaxation measurements needed to calculate the rate constants has not been solved without the expedient of using: 1) volume-averaged, unlocalized measurements; and/or 2) acquiring M'_0 or M_0 under partially saturated conditions (19,21,22,24); or by 3) measuring relaxation in separate studies of other cohorts of subjects (20,23). These expediciencies are troublesome because they assume spatially uniform T_1 and T'_1 and necessitate volume-averaged saturation corrections to M'_0 and M_0 . Alternatively

they assume that T_1 and T_1' measured in separate studies are valid for the potentially different study in question, significantly compounding and extending the study design.

We present here a new fast method of measuring reaction rates with saturation transfer, which avoids these expediciencies and assumptions and allows a complete measurement of the rate constants with just four acquisitions, each performed under conditions that yield 70–79% of the maximum achievable Ernst-angle SNR (25). The technique is based on the efficient dual-angle method of measuring T_1 using a pair of sequences applied with two different flip angles (26). Here, the sequence pair is applied twice, with chemical selective irradiation, and with control irradiation to create the four-angle saturation transfer (FAST) method. We further introduce “FASTER” and “FASTest” protocols for dynamic studies wherein [PCr] and/or k_f may change. With these protocols, one or two of the four acquisitions are omitted and missing information is restored using a new algorithm and data from the initial FAST experiment.

The methods are validated theoretically using the Bloch equations modified for two-state chemical exchange modeled for CK metabolism in skeletal and heart muscle. Potential errors in the rate measurements that may arise from spillover irradiation of PCr, incomplete saturation of the γ -ATP, and the effects of exchange on the calculated values of M_0' , M_0 , and T_1' (27) are evaluated. In experimental studies, we demonstrate that the FAST method yields unlocalized measurements of the CK rate constant in the resting human leg with accuracy comparable to conventional saturation transfer measurements, but an order of magnitude faster, and we test the FASTER algorithm. Finally, we combined the FAST method with localized ^{31}P MRS in humans, yielding localized measurements of k_f consistent with the unlocalized measurements in about 20–40 min at 1.5 T.

THEORY

The efficiency of magnetization transfer experiments would be greatly improved if all experiments could be performed under partially saturated conditions with shorter pulse repetition values (TRs) and flip angles approaching the Ernst-angle condition, and if the number of acquisitions required for the T_1 experiments were minimized. If the reaction rates are to be determined from Eqs. [1] and [2] for saturation transfer, then these partially-saturated experiments would first have to reliably predict the fully-relaxed ratio M_0'/M_0 . The fully-relaxed values of M_0 and M_0' could in fact be calculated from the partially-saturated signals, M and M' , acquired in the absence and presence of saturating irradiation by inverting the standard expression for the partially-saturated steady-state signal excited by a series of θ pulses (28):

$$M_0' = \frac{M'(1 - \cos \theta \cdot \exp(-T_R/T_1'))}{[1 - \exp(-T_R/T_1')] \sin \theta} \quad [3]$$

$$M_0 \approx \frac{M(1 - \cos \theta \cdot \exp(-T_R/T_1))}{[1 - \exp(-T_R/T_1)] \sin \theta}. \quad [4]$$

Equation [4] is approximate to the extent that chemical exchange alters the value of M_0 from that predicted by the partially-saturated measurements of the observed T_1 (27). We shall examine this approximation later. Equation [3] makes the standard assumption that during the saturation of γ -ATP, the magnetization can be characterized by a single relaxation time, T_1' .

Since T_1' is the only other variable needed to solve Eq. [1], the entire problem of measuring the k 's under rapid, partially-saturated conditions hinges on determining the T_1 's in the absence and presence of γ -ATP saturation.

FAST Experiment

Arguably, the most efficient method of measuring T_1 to date is the dual-angle method, which yields 70–79% of the maximum achievable Ernst-angle SNR over a broad range of operating conditions, $0.1 \leq TR/T_1 \leq 1$ (26). This method requires the application of just two excitation sequences: one with a flip angle of $\alpha \sim 15^\circ$, and the second with $\beta \sim 60^\circ$, for each T_1 determination. Preferably, the pulses are implemented as adiabatic B_1 -independent rotation (BIR-4) pulses (29), or as BIR-4 phase-corrected (BIRP) pulses, which provide precise flip angles without requiring calibration for each experiment (30). Using the dual-angle method with γ -ATP saturated, T_1' is given by

$$T_1' = -T_R / \ln \left[\frac{\sin \alpha - R' \cdot \sin \beta}{\cos \beta \cdot \sin \alpha - R' \cdot \cos \alpha \cdot \sin \beta} \right] \quad [5]$$

with $R' = M'(\alpha)/M'(\beta)$, the ratio of the partially-saturated PCr signals acquired with the two flip angles. T_1 is given by the same expression without the primes.

Substituting primed or unprimed versions of Eq. [5] in Eqs. [3] and [4] yields (after some rearrangement):

$$M_0 = \frac{M(\alpha) \cdot [\cos \beta - \cos \alpha]}{\sin \alpha \cdot [\cos \beta - 1] - R \cdot \sin \beta \cdot [\cos \alpha - 1]}, \text{ or} \quad [6]$$

equally $\frac{M(\beta) \cdot [\cos \alpha - \cos \beta]}{\sin \beta \cdot [\cos \alpha - 1] - \sin \alpha \cdot [\cos \beta - 1] / R}.$

The expression for M_0' is the same with M' and R' replacing the unprimed values. Equation [5] and primed and unprimed versions of Eq. [6] fully determine M_0' , M_0 , and T_1' for the saturation transfer experiment, and the values therefrom can be substituted in the standard equations (Eqs. [1] and [2]) to calculate both rate constants.

This FAST experiment requires only four experiments: two acquisitions with flip angles of ostensibly 15° and 60° with saturating irradiation applied to γ -ATP, and two control acquisitions with the same flip angles. Note that while 15° and 60° pulses provide excellent SNR performance and T_1 resolution over a broad range of operating conditions, other flip angle combinations can be chosen to optimize performance under specific operating conditions, as described earlier for the dual-angle T_1 method (26). In general, the values of TR, α , and β should be chosen to provide T_1 measurements of reasonable accuracy with high SNR, with TR preferably comparable or less than T_1 or T_1' (26). Because $T_1' < T_1$ for PCr in the CK experiment, different TR values and/or flip angles could conceivably be used for each pair of control and γ -ATP irradiation experiments.

A by-product of the FAST experiment, which is not provided by the conventional saturation transfer experiment, is the observed metabolite T_1 's. These can be determined from the control experiment using the unprimed form of Eq. [5]. In the absence of any spillover irradiation affecting the metabolite resonance during the control acquisitions, these T_1 's should agree with the observed metabolite values measured by conventional T_1 experiments (18). However, as discussed below, the presence of spurious or spillover irradiation shortens them.

Effect of Chemical Exchange on the Value of M_0 Calculated From Eq. [4]

Equations [4] and [5] (for T_1) assume a single exponential model for T_1 that is based on a solution of the Bloch equations that ignores the effects of chemical exchange and is therefore not strictly valid. We previously evaluated the errors in ^{31}P MRS metabolite M_0 values calculated by applying relaxation corrections assuming the single-exponential model in the presence of two-, three-, and four-site chemical-exchange models, over a range of flip angles and TR values that provide near-optimum SNR (27). For two-site exchange, that analysis showed that the error in the saturation factor, and therefore the predicted equilibrium magnetization calculated from Eq. [4] using a dual-angle determination of T_1 , is less than 5% for conceivable values of the chemical-exchange rates $0 \leq k_f \leq 1.5 \text{ s}^{-1}$ and flip angles that deliver useful SNR per unit time over the range $T_1/5 \leq \text{TR} \leq 2T_1$ for skeletal and cardiac muscle. Thus, under these conditions, the error in M_0'/M_0 in Eq. [1] that results from ignoring chemical exchange effects in the Bloch equations would also be less than 5%.

To validate that Eqs. [5] and [6] in conjunction with Eq. [1] are indeed consistent with the Bloch equations modified for two-site chemical exchange, we performed a numerical simulation of the entire FAST experiment based on the modified Bloch equations in a matrix formulation as detailed in the Appendix. CK metabolism was modeled with $k_{AB} = k_f$ and $k_{BA} = k_r$ in two tissue types at 1.5 T (27): 1) skeletal muscle with $T_{1A}^* = T_1^*(\text{PCr}) = 6.7 \text{ s}$, $T_{1B}^* = T_1^*(\gamma - \text{ATP}) = 2.3 \text{ s}$, $[\text{PCr}] \leq 28 \text{ } \mu\text{mol/g wet wt}$, $[\text{ATP}] = 4.5 \text{ } \mu\text{mol/g wet wt}$, $\text{TR} = 1 \text{ s}$; and 2) heart muscle with $T_{1A}^* = 6 \text{ s}$, $T_{1B}^* = 2 \text{ s}$, $\text{PCr}/\text{ATP} \leq 1.5$, and $\text{TR} = 1 \text{ s}$, where T_1^* is the so-called “intrinsic T_1 ” that would be measured if there were no exchange. For both tissues, $T_{2A}(\text{PCr})$ was 0.1 s and $T_{2B}(\text{ATP})$ was 0.05 s. For this simulation, the effects of off-resonance irradiation of PCr and of incomplete saturation of γ -ATP were minimized by assuming a 15T static magnetic field strength and a selective RF pulse power of 15 Hz (0.87 μT). Off-resonance and incomplete saturation effects are addressed later. The modified Bloch equations were iterated for a period of about three times the longer T_1^* of the two exchanging moieties, and the values of $M'(\alpha)$, $M'(\beta)$, $M(\alpha)$, and $M(\beta)$ were recorded. These were substituted in Eqs. [5] and [6] to calculate M_0' , M_0 , and T_1' , which in turn were substituted in Eq. [1] to calculate the k_f that would result from the FAST method. This value was compared with the model value. The simulation was performed for both model tissues over the range $0.05 \leq k_f \leq 1.0 \text{ s}^{-1}$ with up to a 10-fold depletion of [PCr].

The results are shown in Fig. 1. In Fig. 1a, all of the FAST k_f values for muscle at all of the PCr concentrations are indistinguishable from the true values. Contour plots of the relative error in k_f for the two tissues in Fig. 1b and c reveal that the maximum error in k_f is 5% or less. This analysis indicates that the FAST solution is consistent with the modified Bloch equations for two-site exchange, and that any effect that chemical exchange has on the calculation of M_0' and M_0 from Eqs. [5] and [6] is of negligible consequence to the computation of k_f in this range of examples.

Omitting Acquisitions From Repeat k Measurements During Dynamic Studies

Completing a magnetization transfer measurement of k is much more difficult when the metabolite concentrations and/or chemical-exchange rates change during the course of a study involving some experimental perturbation. Obviously, the calculation of k 's from Eqs. [1] and [2] assume that T_1' , M_0' , and M_0 are all measured at the same time, which is not physically possible with current methods. Thus, the experiments to measure each k must be completed within a period during which T_1' , M_0' , and M_0 do not change appreciably, a situation now much

more easily accomplished with the reduced number of acquisitions permitted by the FAST method. But perhaps this is still not fast enough.

It is prudent to ask, in a dynamic study in which k , M_0' , and M_0 may change in response to intervention, whether any of the four acquisitions in a repeat FAST experiment could be omitted without seriously compromising the accuracy of the determination of the k 's. For example, if one or both of the 15° acquisitions, which generate lower SNR and may require longer averaging, could be omitted, the measurement time for this repeat experiment could be done in half or less, of the time required for the initial FAST experiment. In this case, the new values of T_1' and T_1 needed to calculate M_0' , M_0 , and k would have to be derived somehow from the initial complete FAST experiment.

We show below that omitting the 15° control acquisition in a repeat experiment is conceivable if we assume (assumption 1) that (unprimed) T_1 , or, more specifically, the saturation factor calculated from T_1 , is not appreciably affected by the dynamic changes in M_0 or chemical exchange relative to the initial FAST experiment. In addition, omission of the 15° γ -ATP saturated acquisition is conceivable if we assume (assumption 2) that the intrinsic T_1 , T_1^* , does not change significantly from the initial FAST experiment. This latter assumption is actually standard practice for magnetization transfer MR.

Omitting the Control 15° Acquisition

Assumption 1 is troublesome in that large effects of chemical exchange on T_1 can arise when M_0 varies significantly during the course of an experiment, as noted earlier (27). Thus, the error in the value of M_0 calculated from Eq. [4] using a new value of M determined from a later experiment in a dynamic study, plus the original value of T_1 , depends on the magnitude of the changes in M_0 and k_f , and the T_1^* of the exchanging species. It can be calculated for two-site exchange using eqs. 2–10 and 17 of Ref. 27, or, as done here, by iterating the exchange-modified Bloch equations in the Appendix. Again, we minimize the effects of spillover PCr irradiation and incomplete γ -ATP saturation by choosing a 15 T field strength and 15 Hz saturating field.

Figure 2a shows the effect of up to a fourfold (or 75%) depletion of [PCr] on the T_1 observed by a complete FAST experiment in model muscle over the conceivable range of in vivo biological k_f values, with TR = 1 s and 2 s. Chemical exchange with $k_f = 1 \text{ s}^{-1}$ causes the observed $T_1(\text{PCr})$ to decrease by 35–38% from the chosen intrinsic value of 6.7s (27), down to 4.2–4.4 s when PCr is depleted to 25% of its initial value. This is larger than the 20% reduction to about 5.4 s that would be observed in an initial complete FAST experiment with an undepleted [PCr] of 28 $\mu\text{mol/g}$ and $k_f = 1 \text{ s}^{-1}$. It is the difference between these two T_1 values that introduces errors into new calculations of M_0 in the depletion experiment, as would result, for example, if a value of 5.4 s were used for T_1 instead of the correct value of 4.3 s which would be unavailable if the control 15° acquisition were dropped.

The error in the value of M_0 calculated from the initial (wrong) value of T_1 and the partially saturated/depleted value of M is plotted in Fig. 2b for measurements performed at TR = 1 and 2 s, assuming k_f remains constant. It is less than 8% for up to 50% PCr depletion, and less than 15% for a 75% depletion in this example. However, because of the nature of Eq. [1], this error in M_0 often propagates to a smaller percentage error in k_f for $k_f = 1$. For example, with $k_f = 0.3 \text{ s}^{-1}$ and $T_1' = 2 \text{ s}$, the error in k_f resulting from this error in M_0 that occurs as a consequence of omitting the control 15° acquisition is only about 3% after PCr has been depleted by 50%, and 5% with 75% of the PCr depleted. Thus, omission of the control 15° acquisition will often

be tolerable for FAST dynamic in vivo ^{31}P MRS CK studies in which PCr is depleted by up to 50% or more in the period following the last determination of $T_1(\text{PCr})$.

Omitting the 15° Acquisition in Which $\gamma\text{-ATP}$ Is Saturated

If the 15° $\gamma\text{-ATP}$ saturated acquisition is also unavailable in a repeat study in which M_0 varies significantly, a new value of T_1' , and consequently a new M_0' , can still be estimated based on the more robust assumption 2, that T_1^* is unaffected by chemical exchange. T_1^* is first determined from measurements acquired in the initial FAST experiment. It is given by (24):

$$T_1^* = T_1' M_0 / M_0'. \quad [7]$$

Because T_1^* is constant, if M_0/M_0' changes after the initial experiment, T_1' must also change proportionately. For the i^{th} experiment to measure k_f in a dynamic study, the new value of T_1' is:

$$T_1^{i'} = T_1^* M_0^{i'} / M_0^i. \quad [8]$$

Although T_1^* in Eq. [8] is now known from Eq. [7], the fully-relaxed ratio $M_0^{i'} / M_0^i$ remains unknown because only a partially saturated ratio, $M^{i'}(\alpha)/M^i(\alpha)$ is available from the two acquisitions of the i^{th} experiment. However $T_1^{i'}$ can be determined iteratively as follows.

We calculate a first approximation of $T_1^{i'}$, $T_1^{i,1'}$, by substituting $M^{i'}(\alpha)/M^i(\alpha)$ for $M_0^{i'} / M_0^i$ in Eq. [8]. A first estimate of the equilibrium magnetization, $M_0^{i,1'}(T_1^{i,1'})$ from Eq. [3] is then computed using this first $T_1^{i,1'}$. We also calculate $M_0^i(T_1)$ from either 1) Eq. [4] using the value of T_1 from the initial FAST experiment if the 15° control acquisition is unavailable, per the previous section; or 2) Eq. [6] if both the control 15° and 60° acquisitions are available. An updated ratio of magnetizations, $M_0^{i,1'}(T_1^{i,1'}) / M_0^i(T_1)$ is again substituted in Eq. [8] to generate a second approximation of $T_1^{i'}$, $T_1^{i,2'}$. The iteration is repeated until the difference between consecutive estimates, $(T_1^{i,(n+1)' } - T_1^{i,n' })$, is less than a small error, ϵ , at which point $T_1^{i'}$ is equated to $T_1^{i,(n+1)' }$, and $M_0^{i'}$ to $M_0^{i,(n+1)' }$. Because Eqs. [3] and [4] are fairly smooth, well behaved functions, the iteration converges fairly rapidly. Finally, the numerically calculated $T_1^{i'}$, $M_0^{i'}$, and M_0 are substituted in Eqs. [1] and [2] to calculate the new values of k . A schematic diagram of this FASTER algorithm is depicted in Fig. 3.

The relative error between the true value of k_f and the value that results from applying the FASTER algorithm to calculate $T_1^{i'}$ and $M_0^{i'}$ for an experiment in which $M_0(\text{PCr})$ changed by 10-fold was computed by iterating the exchange modified Bloch equations in the Appendix (again neglecting spillover irradiation and incomplete $\gamma\text{-ATP}$ saturation) to generate values of $M'(\alpha)$, $M(\alpha)$, and $M(\beta)$. These values were then input to the FASTER algorithm, as described above, to generate new estimates of k_f .

The results, which incidentally include the potential exchange-related errors in the FAST method discussed previously, are plotted in Fig. 4 for model skeletal and heart tissue CK metabolism for $0.05 \leq k_f \leq 1.0 \text{ s}^{-1}$. While the algorithm shows signs of cracking at extreme values of k_f and M_0 , it is basically sound over a very broad range of operating conditions, since in both model tissues the absolute error in k_f does not exceed 0.02 s^{-1} over the plotted range. This error will generally not be significant for in vivo dynamic saturation transfer experiments. Therefore, it should be permissible to omit the $\gamma\text{-ATP}$ -saturated 15° acquisition in dynamic

studies of heart and skeletal muscle in which the T_1^* values are comparable to those modeled here over the entire range of conditions presented in Fig. 4.

FASTer and FASTEST Strategies

From a comparison of Figs. 2b and 4 it is observed that the errors that result from omitting the γ -ATP-saturated 15° acquisition using the FASTer algorithm are, for the same change in M_0 , less than those produced by omitting the control 15° acquisition and assuming that the initial T_1 is unchanged. Therefore, it is reasonable to consider two strategies to expedite k_f measurements in a dynamic experiment in which M_0 changes following an initial complete FAST measurement, and when there is insufficient time to repeat a full FAST experiment.

The first strategy, the FASTer protocol, would involve dropping the 15° γ -ATP-saturated acquisition during the dynamic portion of the study, resulting in a three-acquisition experiment comprised of the two control acquisitions and a single acquisition with γ -ATP saturated. Typical errors in k_f are $= 0.02 \text{ s}^{-1}$ (Fig. 4) when the FASTer algorithm is used to restore the missing information.

In the second strategy, the FASTest protocol, both of the 15° acquisitions are dropped during the dynamic portion of the study. This results in just a two-acquisition experiment. The iterative algorithm is used to calculate $T_1^{i'}$ and $M_0^{i'}$. The original T_1 is assumed for calculating M_0 in the absence of the control 15° acquisition, giving rise to the errors that propagate from Fig. 2, which are much greater than those in Fig. 4 that arise from dropping the 15° γ -ATP-saturated acquisition. Thus, from Fig. 2b, the errors in dropping both 15° acquisitions are generally less than 8% if M_0 is not depleted much more than 50% since the time that T_1 was last determined. Although there is a tiny error contribution from dropping the 15° γ -ATP-saturated acquisition, this estimate is conservative because of the way the 8% error propagates to k_f , as discussed in the above section on omitting the control 15° acquisition.

Effects of Spillover Irradiation of PCr and Incomplete Saturation of γ -ATP

In practice, if the selective irradiation applied to the γ -ATP resonance is not perfectly adjusted, it may also affect the PCr resonance due to its close proximity. Typically, the irradiation reduces the amplitude of PCr by partially saturating it. In the conventional saturation transfer experiment, it is customary to address this problem by conducting the control experiment with the same selective irradiation symmetrically applied to the opposite side of the PCr resonance. It is commonly assumed that the effect of any spillover irradiation of PCr is thereby neutralized because it will be the same for both acquisitions. However, this assumption can introduce errors in the calculated rate constants, primarily from two sources (31–37). First, in the control experiment in the presence of spillover irradiation, the PCr signal is greater than it would be in the absence of chemical exchange because the spillover-affected PCr is being partially replenished by unsaturated spins from the γ -ATP (31–33). Second, the spillover irradiation reduces the observed T_1' and T_1 of PCr (34–37). This occurs because the spillover irradiation imparts an extra flip angle to the PCr that is not accounted for in the T_1 calculations. Although this irradiation generates no transverse magnetization, it does knock out some longitudinal magnetization, altering the apparent T_1 by moving the steady-state condition along the relaxation curve. Consideration of Eq. [1] shows that in the standard experiment, spillover irradiation typically decreases the value of k_f measured by the standard experiment relative to the true value, as the strength of the irradiation increases.

In the FAST experiment, we adopt the same protocol for performing the control experiments—in this case the two acquisitions with flip angles of 15° and 60° , in the presence of identical saturating irradiation applied to the opposite side of the PCr resonance to γ -ATP. As in the conventional saturation transfer experiment (34–37), the spillover irradiation reduces the

apparent T_1' . It also reduces the value of T_1 of PCr that can be calculated from the unprimed version of Eq. [5], compared with the value of T_1 observed in the absence of any saturation, or with literature values of T_1 (18). Consequently, spillover irradiation affects the values of M_0 and M_0' derived from Eq. [6]. Thus, the errors in k_f measured by the FAST method due to spillover irradiation will differ from those in the standard method inasmuch as the FAST method calculates M_0 and M_0' from the spuriously altered T_1 values, whereas M_0 and M_0' are measured directly under fully-relaxed conditions in the conventional method. Since both methods require measurements of T_1' for Eq. [1], the error in T_1' caused by spillover irradiation should be comparable for both methods.

Kingsley and Monahan (35–37) recently analyzed the errors in k_f for the CK system introduced by spillover irradiation and incomplete saturation of γ -ATP in the conventional saturation transfer experiment performed under fully-relaxed conditions, using the Bloch equations modified for chemical exchange. They found that the standard equation (Eq. [1]; their eq. 35), underestimates k_f by up to 18% in the presence of spillover irradiation of PCr, with field strengths of up to 120 rad/s (19 Hz) for $k_f = 0.5 \text{ s}^{-1}$ during control experiments (37). One solution to correct the problem (33) was worse than not using any correction, producing a 64% error with field strengths of up to 120 rad/s (37). Except for experimental protocols that stop chemical exchange for the control experiment (31), which are impractical in vivo, the analysis showed that, to date, the most accurate correction for spillover irradiation of PCr and incomplete saturation of γ -ATP is to replace Eq. [1] with

$$k_f T_1' \approx \frac{Q(1 - M_0'/M_0)}{U - V}. \quad [9]$$

This is eq. 27 of Ref. 37, in which we have substituted Q for the ratio of M_0 measured with control irradiation to that measured with the control irradiation switched off; U for the ratio of the equilibrium magnetization of γ -ATP in the control saturation experiment to that recorded without any saturation; and V for the ratio of the equilibrium value of the residual magnetization of γ -ATP recorded while γ -ATP is being irradiated, to that recorded without any saturation.

To compare the performance of the FAST method with the standard method, and to extend Kingsley and Monahan's analysis of the situation wherein too much or too little saturating irradiation is applied to γ -ATP during the FAST experiment, the chemical-exchange modified Bloch equations described in the Appendix were evaluated for model skeletal and cardiac tissue CK metabolism at 1.5 T, for $0 \leq k_f \leq 1 \text{ s}^{-1}$. The analysis was performed with saturating irradiation field strengths up to 10 Hz (or 62 rad/s), which corresponds to Q values in the approximate range $1 \geq Q \geq 0.5$, that is, up to a 50% attenuation of PCr in the control experiments due to spillover irradiation. The effect of replacing Eq. [1] with Eq. [9] was also evaluated for both methods. For the FAST method, we defined Q as the ratio of M_0 measured with control irradiation to that measured without any irradiation, as calculated from Eq. [6] using the partially saturated experiments. In this way, the evaluation for FAST includes the additional effects of spillover irradiation on both T_1 and T_1' that are propagated to M_0 and M_0' .

The results for skeletal muscle and heart tissue are shown in Figs. 5 and 6, respectively, for saturating field strengths of 2.5 Hz ($Q = 0.94\text{--}0.99$), 5 Hz ($Q = 0.77\text{--}0.91$), and 10 Hz ($Q = 0.47\text{--}0.72$). Errors produced by spillover irradiation and/or incomplete saturation manifest as deviations from the unity line (dashed). The errors in k_f that result from incomplete saturation of γ -ATP are about the same for both skeletal muscle (Fig. 5a and d) and heart (Fig. 6a and d) when Eq. [1] is deployed, although the FAST method appears to be more accurate than the standard method when Eq. [9] is used. At Q values of 0.8–0.9 saturation is near-optimum for 1.5 T (Figs. 5b and e, and 6b and e), and the accuracy of both methods is improved. The FAST method is less accurate than the standard method when Eq. [1] is used, although Eq. [9] renders

comparable accuracy for both methods. The errors in FAST are $\leq 7\%$ for $0 \leq k_f \leq 0.7 \text{ s}^{-1}$ for heart, and about 6–8% for skeletal muscle, using both methods at $k_f = 0.5 \text{ s}^{-1}$. The accuracy of the FAST method deteriorates with excessive spillover saturation of PCr corresponding to Q values of 0.5 and lower (Figs. 5f and 6f), due primarily to the effects of the T_1 error on M_0 . Nevertheless, Eq. [9] still yields accurate results for FAST up to $k_f = 0.5 \text{ s}^{-1}$ with $Q = 0.5$ or half of the PCr knocked out by spillover irradiation. In both model tissues, the errors are largest when [PCr] is at a maximum with respect to [γ -ATP], as depicted in Figs. 5 and 6. The errors are less with lower PCr/ γ -ATP ratios, or as [PCr] depletes.

These results show that 1) the performance of the FAST method in the presence of spillover irradiation and incomplete irradiation of γ -ATP is generally comparable to the conventional method, particularly at the higher Q values; and 2) the modified Kingsley-Monahan Eq. [9] also improves the accuracy of FAST at higher k_f values.

EXPERIMENT

Proton (^1H) MRI and ^{31}P MRS experiments were performed on a 1.5 T whole-body GE Signa scanner equipped with broad-band spectroscopy and a ^{31}P 6.5-cm-diameter surface receiver coil and 25-cm-diameter ^{31}P transmitter coil. All ^{31}P MRS experiments were performed using 4-ms BIRP adiabatic excitation pulses to ensure precise flip angles without having to calibrate them for each study (30). A continuous square pulse at 2% of the maximum ^{31}P MRS power level was chosen to provide a chemical-selective saturation field strength of 5–10 Hz over the sensitive volume of the detector coil, at levels that were within the U.S. Food and Drug Administration (FDA) power deposition guidelines for the specific absorption rate. The square saturation pulse was switched off during the BIRP excitation pulse and data acquisition window. Trains of sinc-modulated pulses and hyperpulses (38) were also investigated for this purpose, but were rejected because their frequency selection was inferior, resulting in low values of Q in phantom studies. The 2% pulse amplitude was the minimum required to provide complete saturation of γ -ATP at -2.7 ppm relative to PCr in repeated in vivo experiments. This, and tuning the saturation frequency, were verified by visual inspection of the unlocalized ^{31}P spectrum in each study. Control irradiation was applied at 2.7 ppm. All ^{31}P data acquisitions were preceded by a train of dummy excitations lasting 16–20 s, to ensure the establishment of steady-state equilibrium.

Calf-muscle studies were used to test whether the FAST method yields the same values of the CK rate constants as the conventional fully-relaxed saturation transfer method. The data were also used to check whether the FASTER algorithm could calculate the same k_f from T_1^* when a 15° acquisition is dropped. These studies were performed on the calf muscle of 10 healthy volunteers (four females, six males, 36–55 years old, mean 43 ± 6 years) who provided informed consent under an institutional review board-approved study. Because the scan time required to perform both a fully localized, fully relaxed conventional saturation transfer study and a FAST study in the same exam was prohibitive, the performance of the FAST method relative to the conventional method was first performed in unlocalized experiments. After positioning subjects in the scanner, automatic shimming and conventional transaxial ^1H MRI were performed through the center of the ^{31}P coil set, to confirm coil location relative to the anatomy and to optimize magnetic field homogeneity.

For the conventional saturation transfer experiments, the fully-relaxed values of M_0 and M_0' were measured with TR = 20 and 16 s. T_1' was measured by the partial saturation method applying 90° BIRP pulses and acquiring spectra at TR = 0.6, 1, 1.5, 2, 3, 4, 8, 12, and 16 s while continuously irradiating γ -ATP. Twelve to 64 free induction decays (FIDs) were averaged for each TR value. Spectra were fitted to obtain peak areas using Magnetic Resonance User Interface (MRUI) time-domain fitting software (available from <http://carbon.uab.es/>)

mrui). In cases where time-domain fitting yielded nonsense results, spectra were fitted with Gaussian functions in the frequency domain via a simplex method. As parameters were determined from ratios of signals, this had no noticeable effect on the results. T_1' was calculated using a three-parameter least-squares fit to the varying-TR data:

$$M_0' = M_0' \{1 - B \exp(-T_R/T_1')\} \quad [10]$$

with B , a constant. The observed T_1 is not needed to calculate the k 's, and this conventional experiment does not yield it. Unlocalized FAST was then performed with TR '1 s and saturation pulse = 0.82 s. Thirty-two FIDs were averaged for each of the four FAST pulse sequences: two acquisitions with γ -ATP saturated employing 15° and 60° flip angles, and the two control acquisitions with 15° and 60° flip angles.

Spatially-localized FAST saturation transfer experiments were next performed on the calf muscle in separate studies of six of the volunteers by adding a 1D phase-encoding gradient pulse after the BIRP pulse, as depicted in fig. 1a of Ref. 22. These experiments were performed with 32 phase-encoding steps and 1-cm resolution perpendicular to the coil plane. Eight to 24 FIDs were averaged for the 15° excitations, and 8 or 12 FIDs were averaged for the 60° excitations, requiring about 4–13 min and 4–6.5 min per data set, respectively, for a total acquisition time of 17–39 min. These spectra were curve-fitted as above and used to calculate rate constants for comparison with the unlocalized FAST and conventional measurements. In several experiments, an additional 12-FID 60° flip angle data set was acquired with the saturation switched off in order to measure Q .

RESULTS

Figure 7 shows complete unlocalized data sets acquired by the conventional saturation transfer method (Fig. 7a–c), and by the FAST method (Fig. 7d and e) from the same leg during the same session with comparable SNR. The values of k_f and T_1' were 0.23 s⁻¹ and 2.3 s, as determined from Eqs. [1], [5], and [6] for FAST, in agreement with values of 0.22 s⁻¹ and 2.1 s for the conventional method obtained with Eqs. [1] and [9], respectively. For the 10 subjects studied by both methods in the unlocalized experiment, the FAST method yielded rate constants in about 3 min compared to over 21 min for the conventional method—seven times faster!

The rate constants k_f and k_r calculated from Eqs. [1] and [9], relaxation times (T_1'), and fully relaxed ratios of PCr/ATP and M_0'/M_0 for PCr for the two methods, averaged for the 10 subjects, are tabulated in Table 1. The mean value of Q used for Eq. [9] was 0.86 ± 0.01 , which corresponds to a spillover irradiation of PCr in the range shown by the Bloch equation analysis to provide accurate k_f values (Fig. 5). There was no significant residual γ -ATP signal evident in the γ -ATP saturated spectra ($V = 0$). The table shows that there is no significant difference in the results measured by the standard and FAST methods, and that the uncertainties (SD) are essentially the same. The use of Eq. [9] (from Kingsley and Monahan (37)) did not significantly alter the k_f estimates. The mean values of M_0 and M_0' calculated by the FAST method were slightly lower than the measured fully-relaxed values from the conventional experiment by similar proportions (the ratio of FAST M_0 to the measured M_0 was $92\% \pm 9\%$, and $95\% \pm 11\%$ for M_0'), although their ratios are not significantly different (Table 1).

Figure 8 shows a complete spatially-localized FAST ³¹P MRS data set from the human leg, and a corresponding ¹H image. In this set, the mean FAST k_f calculated from Eq. [1] is 0.23 ± 0.04 s⁻¹ excluding the most superficial spectra. Figure 9 shows that in the six subjects studied with localized FAST there is no significant variation of k_f with depth through the calf muscle. This indicates that the excitation field is rendered effectively uniform by the use of the adiabatic

BIRP pulses (30). The average of the mean FAST rate constants for the six subjects are summarized in Table 1. The values do not differ significantly from the unlocalized FAST values, or from the conventional measurements.

To test whether the FASTer algorithm could accurately calculate k_f from T_1^* when the γ -ATP-saturated, 15° acquisition is omitted from subsequent experiments, T_1^* was first calculated from Eq. [7] for each of the 10 unlocalized complete FAST experiments. The algorithm (Fig. 3) was then applied to the three FAST acquisitions of the same data set, dropping the 15° acquisition, and the values of the missing M_0' and T_1' were compared with actual values determined from the full FAST experiment. The results for each iteration are plotted in Fig. 10. The curves show that although the algorithm started with deviations of 15–65% from the correct values, it converged to within 1% or less of the correct values of M_0' and T_1' within seven iterations in all 10 cases.

DISCUSSION

The time required to complete a measurement critically impacts the feasibility of MRI/MRS studies performed in vivo. Experience with human studies indicates that the tolerable total exam time is limited to about an hour, essentially prohibiting clinical studies of disease with protocols much longer than this. The conventional saturation transfer experiment is inefficient because of the time spent waiting for a fully-relaxed measurement of M_0 and M_0' , and because of the disproportionate amount of experimental time that is spent measuring T_1' . Thus, the measurement of CK flux rates that are localized to high-energy-consuming organs in humans in vivo is essentially impractical at clinical field strengths using the conventional saturation transfer method, because of the large number of localized and fully relaxed acquisitions required.

In this work we introduced a new method, FAST, for measuring reaction rate constants requiring just four acquisitions applied with two flip angles, ostensibly 15° and 60° , and with irradiation applied to the exchanging species and control irradiation. These flip angles were chosen to optimize SNR performance and T_1 resolution, although other angles can be used (26). Equations for computing k_f and k_r from these acquisitions were derived. This method is much more efficient because all measurements are done under partially-saturated conditions with a T_1' determination based on the same number of measurements as M_0' and M_0 . We analyzed the FAST method using a numerical solution of the Bloch equations in matrix form, modified for two-site chemical exchange. We demonstrated that with negligible spillover irradiation of PCr and complete saturation of γ -ATP at high magnetic field strengths, the method yields correct values of k_f with essentially negligible errors for CK metabolism in model skeletal and heart tissue (Fig. 1). This was accomplished over a broad range of experimental conditions that includes the conceivable range of biological k_f values and the near-complete depletion of PCr.

We further analyzed the effect of dropping the 15° acquisitions after an initial complete FAST experiment in repeat measurements of k_f during dynamic studies in which PCr changes. In the FASTer protocol requiring three acquisitions, the 15° γ -ATP-saturated acquisition is eliminated from the repeat experiment, and a new algorithm is introduced to replace the missing information. Bloch equation analysis showed that this protocol introduces essentially negligible errors of $<0.02 \text{ s}^{-1}$ for up to 90% depletion of PCr in both model skeletal and heart muscle. If the control 15° acquisition is also omitted in the FASTest protocol to provide a two-acquisition repeat experiment, the analysis shows that use of the initial value of T_1 introduces a net error in k_f that is generally less than 8%, provided that the [PCr] change is limited to about 50% or less. FASTest is thus well suited to isometric exercise cardiac stress testing, wherein

the changes in PCr are typically less than 50% (39). If the changes in PCr are more than 50% in a dynamic study, one can devise a protocol whereby an initial FAST experiment is performed, followed by a series of two-acquisition FASTest measurements, with a three-acquisition FASTer experiment included whenever PCr is depleted by 50% in the time since T_1 was last measured. The reduction in scan time compared with the initial FAST experiment that can be achieved by dropping both 15° acquisitions in such dynamic studies can be greater than twofold, because the 15° acquisitions yield significantly lower SNR. Thus, for example, in many of our localized experiments the SNR of the 15° acquisitions was increased by doubling the number of averages compared to the 60° acquisitions. Eliminating both these acquisitions would therefore reduce the scan-time for each k_f determination by threefold compared to FAST.

The main difficulty with saturation transfer experiments in general is the performance of the saturation pulse, especially with the smaller chemical shift dispersions associated with the lower magnetic field strengths of clinical MRI scanners, such as the 1.5 T system used here. The saturating pulse power must be carefully adjusted to yield complete saturation of one of the two exchanging species and yet minimize spillover irradiation of the other peak. Our analysis of the effects of spillover irradiation and incomplete saturation using the exchange-modified Bloch equations showed that the susceptibility of the FAST method to these errors is comparable to that of the conventional saturation transfer method in model skeletal and heart muscle at 1.5 T when the saturation takes out $\leq 23\%$ of the PCr. Performance deteriorates as spillover increases, due to its effect on the observed T_1 's. However, accurate results are possible at higher levels of spillover irradiation for lower values of k_f , for example, with a 50% attenuation of PCr and $k_f \leq 0.2 \text{ s}^{-1}$, but clearly the message is, *do not apply excessive saturating RF power*. This, in any case, may be limited by FDA RF power deposition guidelines. In general, the modified Kingsley-Monahan Eq. [9], developed as a replacement for Eq. [1] to help correct the standard method (37), also improves the accuracy of the FAST method when there is too much or too little saturating irradiation. At higher magnetic field strengths (22, 23), the higher chemical shift dispersion improves the ability to satisfy the condition that γ -ATP be completely saturated while PCr remains unaffected, thereby minimizing these error sources.

The unlocalized experimental studies of human skeletal muscle demonstrated that the FAST method yields the same values of k as the conventional saturation transfer experiment, under the non-ideal conditions of a clinical 1.5 T MRI scanner, with essentially the same uncertainty, an average of seven times faster. This efficiency gain resulted from the omission from the conventional experiment of the many experiments needed to measure T_1 ' and the fully-relaxed values of M_0' and M_0 . Although the standard experiment could perhaps have been hastened by taking advantage of the lower value of T_1' ($< T_1$), this would require prior knowledge, which, for in vivo human studies, is still not reliably available. Nevertheless, the time advantage of the FAST method for comparable SNR is still manifold.

Indeed, localized studies employing the conventional saturation transfer protocol were too time-consuming for human studies in the present work. In contrast, localized FAST data were acquired from human skeletal muscle in 17–39 min, and yielded the same k values as both the unlocalized conventional and FAST experiments. Thus, the timesaving FAST method was truly enabling because it permitted localized saturation transfer experiments to be performed under the clinically-relevant conditions of a 1.5 T scanner, which were otherwise impractical due to intolerably long scan times. Although demonstrated here with 1D localization, FAST can easily be adapted for 2D and 3D chemical shift imaging studies by adding appropriate phase-encoding gradients (22).

The values of $k_f = 0.29 \pm 0.06 \text{ s}^{-1}$ and $T_1' = 1.96 \pm .28 \text{ s}$ for the calf muscle obtained by both conventional and FAST methods are similar to the values of $0.24 \pm 0.08 \text{ s}^{-1}$ and $T_1' = 1.75 \pm .$

11 s reported previously in unlocalized studies of the resting human forearm employing a single 25-mm transmit/receive surface coil and a “pseudo 90° pulse angle” (24). Our studies benefited from the more uniform field provided by the separate larger transmitter coil and the use of adiabatic BIRP pulses, as demonstrated by the constancy of k_f with position in the leg (Fig. 9).

Finally, omission of the 15° γ -ATP-saturated acquisition data from the calculation of k_f and application of the FASTer algorithm yielded the correct missing information with 99% accuracy, within 7 iterations, in all cases. The experiments did not test the FASTer algorithm or the FASTest protocol under a dynamic situation in which [PCr] is changing; these are addressed by the theoretical analysis, as noted above. We are currently employing the FASTest protocol to determine local reaction rates and fluxes in the human heart under pharmacologic stress conditions, and the method appears to deliver consistent results. The total acquisition time during stress is about 13 min. Application of the FASTest protocol to unlocalized skeletal muscle studies would reduce the 3-min FAST acquisitions presented here to about 1 min, with the same SNR.

In conclusion, the FAST method offers new enabling opportunities for the rapid measurement of reaction rate constants by NMR, especially for in vivo studies where scan time is critical. More specifically, its use for studying CK metabolism with ^{31}P MRS in animals and humans may help complete the understanding of the role of CK metabolism in human heart failure, and provide new insights into disorders affecting brain and muscle. With the FASTer and FASTest protocols, dynamic experiments to study the effect of exercise on, for example, human skeletal (24) and heart (22) muscle CK metabolism, or visual stimulation on the human brain (23), are now conceivable without the usual assumptions and concerns about localization or changes in T_1 .

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APPENDIX

The standard saturation transfer and FAST experiments were simulated using a numerical solution to the Bloch equations modified for the chemical exchange of two species in matrix form:

$$\frac{d}{dt}\vec{M} = A\vec{M} + \vec{C} \quad [A1]$$

with general solution:

$$\vec{M} = e^{At}(\vec{M}(t=0) + A^{-1}\vec{C}) - A^{-1}\vec{C} \quad [A2]$$

$$\text{where } \vec{M} = \begin{bmatrix} m_x^A \\ m_y^A \\ m_z^A \\ m_x^B \\ m_y^B \\ m_z^B \end{bmatrix} \text{ and } \vec{C} = \begin{bmatrix} 0 \\ 0 \\ \frac{M_0^A}{T_{1A}} \\ 0 \\ 0 \\ \frac{M_0^B}{T_{1B}} \end{bmatrix}. \quad [A3, A4]$$

For two exchanging species *A* and *B* with resonance offset frequencies ω_A and ω_B irradiated with a constant saturating RF field aligned with the *x*-axis of a frame of reference rotating with frequency ω and strength ω_1 rad/s, the matrix *A* can be constructed from Eqs. [1]–[6] of Baguet and Roby (40): calculations of M_0' , M_0 , the relaxation times, and the exchange parameters.

$$A = \begin{bmatrix} -\frac{1}{T_{2A}} - k_{AB} & \Delta\omega_A & 0 & k_{BA} & 0 & 0 \\ -\Delta\omega_A & -\frac{1}{T_{2A}} - k_{AB} & \omega_1 & 0 & k_{BA} & 0 \\ 0 & -\omega_1 & -\frac{1}{T_{1A}} - k_{AB} & 0 & 0 & k_{BA} \\ k_{AB} & 0 & 0 & -\frac{1}{T_{2B}} - k_{BA} & \Delta\omega_B & 0 \\ 0 & k_{AB} & 0 & -\Delta\omega_B & -\frac{1}{T_{2B}} - k_{BA} & \omega_1 \\ 0 & 0 & k_{AB} & 0 & -\omega_1 & -\frac{1}{T_{1B}} - k_{BA} \end{bmatrix}. \quad [A5]$$

with $\Delta\omega_A = \omega_A - \omega$ and $\Delta\omega_B = \omega_B - \omega$, both in rad/s. Note that the effects of too little or too much, or spillover of the saturating irradiation are accounted for by the ω and ω_1 terms.

The general solution, Eq. [A2], was used to simulate the evolution of the magnetization vectors of exchanging species *A* and *B* during the experiment, by iteration of excitation and acquisition periods with desired values of the saturating field strength and its offset. For our simulations we assumed that the excitation and acquisition periods were too short to significantly impact the results. A pure rotation of the magnetization vector by the desired flip angle about the *x*-axis of the rotating frame was used to simulate the effect of an ideal excitation pulse. At the end of each pulse ($t\alpha^+$), the magnetization is rotated via

$$\vec{M}(t\alpha^+) = \mathbf{R}\vec{M}(t\alpha^-), \quad [A6]$$

where

$$\mathbf{R} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & \cos \alpha & -\sin \alpha & 0 & 0 & 0 \\ 0 & \sin \alpha & \cos \alpha & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & \cos \alpha & -\sin \alpha \\ 0 & 0 & 0 & 0 & \sin \alpha & \cos \alpha \end{bmatrix}. \quad [A7]$$

The magnitude of the transverse magnetization following this rotation was taken as the simulated signal used for calculations of M_0' , M_0 , the relaxation times, and the exchange parameters.

FIG 1.

Comparison of values of k_f measured by the FAST method with true values in model skeletal muscle (**a** and **b**) and heart muscle (**c**) over a 10-fold variation in [PCr] and the range $0.05 \leq k_f \leq 1.0 s^{-1}$. The curves were calculated by iteration of the Bloch equations for two-site exchange in the Appendix for a 15T static magnetic field and a selective RF pulse power of 15 Hz (0.87 μT). **a:** The curves for 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, and 100% of a PCr concentration of 28 mmol/kg wet wt overlie each other and are indistinguishable from the line of identity. Contour plots of the fractional error in k_f measured by FAST compared to the true value are shown as a function of k_f and [PCr] or PCr/ATP in parts **b** and **c**, with grayscale shown at right. Model parameters were:

$T_{1A}^* = T_1^*(\text{PCr}) = 6.7 \text{ s}$, $T_{1B}^* = T_1^*(\gamma - \text{ATP}) = 2.3 \text{ s}$, $[\text{PCr}] \leq 28 \text{ } \mu\text{mol/g wet wt}$, $[\text{ATP}] = 4.5 \text{ } \mu\text{mol/g wet wt}$, $\text{TR} = 1 \text{ s}$, $T_2(\text{PCr}) = 0.1 \text{ s}$ and $T_2(\text{ATP}) = 0.05 \text{ s}$ for skeletal muscle; and for heart, $T_{1A}^* = 6 \text{ s}$, $T_{1B}^* = 2 \text{ s}$, $\text{PCr/ATP} \leq 1.5$, and the same values of TR and T_2 .

FIG 2.

a: The apparent value of T_1 observed by a dual-angle measurement performed at $TR = 1$ s (solid lines) and at $TR = 2$ s (dashed) as a function of k_f , calculated from the exchange-modified Bloch equations for the model muscle tissue with $[PCr] = 28, 21, 14,$ and 7 mmol/kg wet wt, as labeled on the right side. Changes in $[PCr]$ during dynamic studies can cause changes in the value of T_1 , used to calculate M_0 from the FAST method via Eq. [6] which is derived from Eqs. [4] and [5]. **b:** The error in M_0 that results from neglecting these T_1 changes for the different $[PCr]$ depletions, as a function of k_f . The error is what would be expected if the control 15° acquisition were omitted from a repeat experiment during a dynamic study in which PCr is depleted and the original T_1 is assumed, if k_f remains constant.

FIG 3. Schematic diagram of the FASTER algorithm. The algorithm permits calculation of T_1' and M_0' from the values of the intrinsic T_1 , T_1^* , determined in an initial experiment from a dynamic study. This permits omission of the 15° γ -ATP saturated acquisitions in subsequent experiments. Eq, Equation, as numbered in text.

FIG 4.

The absolute error (in s^{-1}) between the true value of k_f and the value that results from applying the FASTER algorithm and the FAST method to calculate T_1' and M_0' for an experiment in which $M_0(\text{PCr})$ changes by 10-fold for (a) model skeletal muscle and (b) model heart muscle. The absolute error in k_f does not exceed 0.02 s^{-1} over the range $0.05 \leq k_f \leq 1.0 \text{ s}^{-1}$. The plots are computed from 800 FAST experiments simulated with the exchange-modified Bloch equations in the Appendix. The result of each experiment was iterated with the FASTER algorithm using the start values indicated by arrows. Spillover irradiation and incomplete γ -ATP saturation were minimized by assuming a 15 T static magnetic field and a saturating field strength of 15 Hz.

FIG 5.

Comparison of the accuracy of (a–c) the standard saturation transfer method with (d–f) the FAST method for measuring k_f in the presence of spillover irradiation of PCr and incomplete saturation of γ -ATP, as computed for model skeletal muscle from the chemical-exchange modified Bloch equations in the Appendix. The vertical axis is the measured value of k_f ; the horizontal axis is the true value. Curves are calculated for on-resonance saturating field strengths of 2.5 Hz or $Q = 0.94$ – 0.99 (a and d), 5 Hz or $Q = 0.77$ – 0.91 (b and e), and 10 Hz or $Q = 0.47$ – 0.72 (c and f) with 1.5 T chemical shift dispersions. Observed k_f values were calculated from Eq. [1] (solid square symbols), or Eq. [9] (circles). The line of equality is dashed.

FIG 6.

Comparison of the accuracy of (a–c) the standard saturation transfer method with (d–f) the FAST method for measuring k_f in the presence of spillover irradiation of PCr and incomplete saturation of γ -ATP, as computed for model heart muscle from the chemical-exchange modified Bloch equations in the Appendix. The vertical axis is the measured value of k_f ; the horizontal axis is the true value. Curves are calculated for on-resonance saturating field strengths of 2.5 Hz or $Q = 0.94$ – 0.99 (a and d), 5 Hz or $Q = 0.77$ – 0.91 (b and e), and 10 Hz or $Q = 0.47$ – 0.72 (c and f) with 1.5 T chemical shift dispersions. Observed k_f values were calculated from Eq. [1] (solid square symbols), or Eq. [9] (circles). The line of equality is dashed.

FIG 7.

Comparison of complete unlocalized data sets acquired by the conventional saturation transfer method (**a–c**), and by the FAST method (**d** and **e**) from the same leg during the same session with comparable SNR. For the conventional method, part **b** depicts a series of spectra acquired at TR values of 0.6–16 s (NEX = 64, 32, 32, 24, 24, 16, 12, 12) with chemically-selective saturation of γ -ATP (arrows), for measuring T_1' . M_0' is determined from the fully-relaxed spectrum at TR = 16 s (NEX = 12). Part **a** shows the peak PCr signals from part **b**, fitted to Eq. [10] to obtain a T_1' value. For the FAST method, part **d** shows two spectra acquired at TR = 1 s with γ -ATP saturated and 15° (lower spectra; NEX = 64) and 60° (upper spectra; NEX = 32) flip angles. **e**: The two corresponding spectra with control irradiation. Adiabatic BIRP pulses were used for the 90°, 60°, and 15° pulses. Steady-state conditions were assumed after applying pulses for ~16 s.

FIG 8.

Conventional transaxial gradient-echo ^1H image of (a) a human leg, showing the location of a ^{31}P MRS detector coil (lower white line) and a series of 1D localized coronal sections (other lines) responsible for a set of spatially-localized FAST ^{31}P spectra shown in b–e. The four sets of spectra are plotted vertically as a function of depth at 1-cm intervals from the coil. Parts b and d were acquired with control irradiation (vertical arrow), with 15° and 60° adiabatic excitation, respectively. Parts c and e were acquired with γ -ATP saturated (vertical arrow), with 15° and 60° pulses, respectively. Each ^{31}P data set was acquired in 4.3 min (NEX = 8; 32 phase-encoding steps) for a total acquisition time of 17 min.

FIG 9.

Mean k_f (filled circles) calculated from Eq. [1] as a function of depth through the calf muscle in the six subjects studied with localized FAST. Error bars are ± 1 standard error.

FIG 10.

Convergence of the FASTER algorithm for calculating correct values of (a) M_0' and (b) T_1' , as tested on the unlocalized human calf muscle spectra from 10 subjects. The γ -ATP-saturated 15° acquisitions were omitted from the data, and M_0' and T_1' were calculated from T_1^* using the algorithm in Fig. 3. M_0' and T_1' converge to within 1% within seven iterations in all cases.

Table 1
Summary of Unlocalized and Localized CK Rate Measurements in Human Calf Muscle

	M_0' / M_0	T_1', s	$k_p s^{-1}$	PCr/ATP	$k_r s^{-1}$
Unlocalized conventional method (n = 10)					
No corrections, Eq. [1]	0.44 ± .06	1.96 ± .28	0.29 ± .06	5.4 ± 1.1	
Corrected with Eq. [9]			0.27 ± .05		1.5 ± 0.2
Unlocalized FAST method (n = 10)					
No corrections, Eq. [1]	0.47 ± .06	1.92 ± .35	0.29 ± .07	5.6 ± 1.0	
Corrected with Eq. [9]			0.29 ± .05		1.6 ± 0.3
Localized FAST method (n = 6)					
No corrections, Eq. [1]	0.51 ± .09	1.74 ± .25	0.29 ± .07	5.4 ± 1.4	
Corrected with Eq. [9]			0.25 ± .08		1.5 ± 0.6