Feasibility Analysis of the Chemical Exchange and T_1 Measurement Using Progressive Saturation (CUPS) Method for In Vivo Application to Human Myocardium

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Target Audience Scientists and clinicians interested in the development and application of ^{31}P MRS for studying cellular energy metabolism.

Purpose Changes in cellular energy metabolism are central in disease of the myocardium[1] and decline of cardiac reserve with aging.[2] The creatine kinase (CK) enzymatic reaction is considered to be important for maintaining ATP supply to energetic demand over the wide operating range of cardiac output.[3] Reduction in CK flux has been observed in humans under a variety of pathological conditions.[4] Accordingly, approaches have been developed and optimized for *in vivo* assessment of CK flux in human myocardium via chemical exchange measurements with ^{31}P MRS.[5] The CUPS method uses a more simplified acquisition compared to magnetization transfer methods, where metabolite T_1's, M_0's, and exchange rates are computed from progressive saturation measurements (e.g. variable TR or flip angle acquisitions) rather than through chemically-selective saturation or inversion. Extensive analysis of the CUPS method has been applied to rodent skeletal and cardiac muscle under preclinical experimental conditions and has shown comparable reliability to saturation transfer methods.[6] The current work extends these previous analyses using both Cramér-Rao lower bound analysis (CRLB) and Monte Carlo (MC) simulations, targeting *in vivo* human MRS conditions for studies of the myocardium at clinical field strength, demonstrating the feasibility of this approach for reliable measurement of CK fluxes under a wide range of experimental and physiological conditions.

Methods The Bloch-McConnell equations incorporating steady-state two-site chemical exchange between phosphocreatine (PCr) and gamma adenosine triphosphate (γATP) are as follows:

$$\frac{d\boldsymbol{M}}{dt} = \boldsymbol{AM} + \boldsymbol{C}, \text{ where } \boldsymbol{M} = (M_{PCr}, M_{\gamma ATP}), \ \boldsymbol{A} = \begin{pmatrix} -\left(\frac{1}{T_{1,PCr}} + k_{PCr,\gamma ATP}\right) & k_{\gamma ATP,PCr} \\ k_{PCr,\gamma ATP} & -\left(\frac{1}{T_{1,\gamma ATP}} + k_{\gamma ATP,PCr}\right) \end{pmatrix}, \text{ and } \boldsymbol{C} = \left(\frac{M_{0,PCr}}{T_{1,PCr}}, \frac{M_{0,\gamma ATP}}{T_{1,\gamma ATP}}\right).$$

The solution for the steady-state magnetization applicable to a spoiled one-pulse ^{31}P MRS acquisition is $\boldsymbol{M}_{ss} = (\boldsymbol{I} - \cos\alpha e^{\boldsymbol{A}TR})^{-1}(e^{\boldsymbol{A}TR} - \boldsymbol{I})\boldsymbol{A}^{-1}\boldsymbol{C}$.[7] A range of tissue T_1's, M_0's, and exchange rates (k) for PCr and γATP were taken from previously published *in vivo* human cardiac studies covering both normative and pathologic conditions [8]; the normative values at 3T were $M_{0,PCr}$=1.7, $T_{1,PCr}$=5.8s, $M_{0,\gamma ATP}$=1, $T_{1,\gamma ATP}$=3.1s, and $k_{PCr,\gamma ATP}$=0.29s^{-1}. Linear and nonlinear spacing of TR values were used under the constraint of synchronous timing with a simulated heart rate. Excitation flip angle α was fixed to 90 degrees. Heart rate was simulated over a range of typical baseline values from 45 to 90 bpm.

Cramér-Rao lower bound analysis provides a theoretical lower bound for the variance of an estimator. If we consider the noise free signal model to be $\boldsymbol{M}_{ss}(\boldsymbol{TR},\boldsymbol{\theta})$ with model parameters $\boldsymbol{\theta}$=[$M_{0,PCr}$, $M_{0,\gamma ATP}$, $T_{1,PCr}$, $T_{1,\gamma ATP}$, $k_{PCr,\gamma ATP}$], and uncorrelated noise σ, the Fisher matrix can be written as $F_{i,j} = \sum_b \frac{1}{\sigma_b^2}\frac{\delta M_{ss,b}}{\delta\theta_i}\frac{\delta M_{ss,b}}{\delta\theta_j}$ over b observations, and the coefficient of variation for a given model parameter can be written as $CV(\theta_i) = \frac{CRLB(\theta_i)}{\theta_i}$ where $CRLB(\theta_i) = \sqrt{(F^{-1})_{ii}}$. This CV represents the precision of the model parameter. Signal-to-noise ratio was defined as $SNR(TR_b) = \frac{M_{0,PCr}\cdot SF(TR_b)}{2\cdot\sigma(TR_b)}$, where $\boldsymbol{SF} = \boldsymbol{M}_0^{-1}\boldsymbol{M}_{ss}\sin\alpha$. SNR was fixed to a constant value between TR's within a given CUPS experiment by adjusting σ(TR_b) through signal averaging, resulting in substantial improvement in measurement reliability.[6] Acquisition times were estimated under all simulation conditions for comparison of acquisition schemes involving differing SNR, number of TR's (*nTR*), and TR values. These estimates were made based on a reference nominal SNR obtained under *in vivo* conditions [5] and using the following:

$$N(TR_b) = \left[\frac{SF(TR_{ref})}{SF(TR_b)}\right]^2 \cdot N(TR_{ref}),$$

which represents the number of signal averages needed to match the SNR of a reference acquisition.

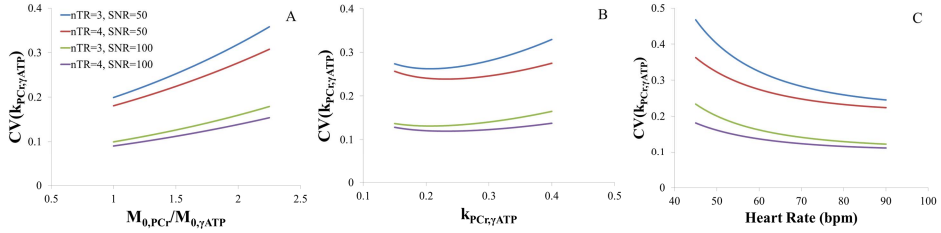

Figure 1. CRLB-derived precision of chemical exchange (CV($k_{PCr,\gamma ATP}$)) using CUPS. Normative input parameters were used with varied (A) metabolite concentration ratio, (B) $k_{PCr,\gamma ATP}$, and (C) heart rate.

Table 1. Accuracy and precision of T_1's and chemical exchange rate from select MC simulations.

SNR	nTR	$T_{1,PCr}$		$T_{1,\gamma ATP}$		$k_{PCr,\gamma ATP}$	
		acc %	prec %	acc %	prec %	acc %	prec %
50	3	-0.2	3.8	-0.1	3.3	-3.3	31.5
	4	-0.4	4.6	-0.1	3.8	-1.9	38.6
100	3	-0.1	1.6	0.3	1.5	-1.4	13.4
	4	-0.3	2.1	0.3	2.0	-2.3	17.1

Monte Carlo simulations combined the noise-free signal, $\boldsymbol{M}_{ss}$, with 100 independent realizations of random Gaussian noise for each set of experimental conditions. MC accuracy was computed as the percent error between the true input simulation parameter value and the mean estimated parameter value over all noise realizations. MC precision was computed as the coefficient of variation of an estimated parameter value over all noise realizations. All analyses were performed using MATLAB (The MathWorks, Natick, MA).

Results and Discussion CRLB analysis showed greater precision and shorter acquisition times when TR values were selected using small integer multiples of the R-R interval with one additional long TR value (e.g. $40 \cdot TR_{R-R}$). There was marginal improvement in $CV(k_{PCr,\gamma ATP})$ with more than three TR values (*Fig.1 nTR=3 vs. nTR=4*); for example, with SNR=100, $CV(k_{PCr,\gamma ATP})$ was reduced from 14% to 12% when including a fourth TR, while the acquisition time was increased by 25%. This negligible difference in parameter reliability between three and four TR values is also apparent from the MC analysis (*Table 1*). In general, for T_1's and M_0's at all simulated SNR levels (e.g. 50, 100, 200), MC analysis showed accuracy and precision within 1.1% and 5.9%, respectively. Both CRLB and MC showed decreased precision of $k_{PCr,\gamma ATP}$ with increasing values of $M_{0,PCr}/M_{0,\gamma ATP}$ (*Fig.1A*). $CV(k_{PCr,\gamma ATP})$ showed a parabolic relationship to $k_{PCr,\gamma ATP}$ with the highest precision occurring ~0.21s^{-1} (*Fig.1B*); this was less pronounced with greater SNR and *nTR*. Unlike precision, the accuracy of $k_{PCr,\gamma ATP}$ from MC simulations showed no clear dependence on the simulated input parameter values but rather a greater dependence on SNR, with accuracy overall within 6.8%, 4.4%, and 0.6% for SNR values of 50, 100, and 200, respectively. CRLB analyses showed decreasing precision in $k_{PCr,\gamma ATP}$ with decreasing heart rate (*Fig.1C*). MC analysis showed a similar relationship between heart rate and $k_{PCr,\gamma ATP}$ precision but did not show any strong relationship between accuracy of $k_{PCr,\gamma ATP}$ and heart rate, with values ranging between 1-3% for SNR values of 50 and 100.

Conclusions CRLB and MC analysis demonstrated important relationships between the reliability of chemical exchange measurements using CUPS and both experimental and physiologic conditions. These relationships are important for the interpretation of *in vivo* experimental results. These initial reliability results and estimated acquisition times demonstrate feasibility for applying the CUPS method to *in vivo* assessment of CK flux in the myocardium.

References *(1) Jennings, R.B et al., Am. J. Pathol. 1981;102:241-255 (2) Hollingsworth, K.G. et al. Am. J. Physiol. Heart Circ. Physiol. 2010;302:H885-H892 (3) Yaniv Y. et al. Tr. Endo. Metab. 2013;24:495-505 (4) Weiss, R.G. et al. PNAS 2005;102:808-813. 5.) Bottomley, P.A. et al. MRM 2002; 47:850-863 (6) Galbán C.J. et al. MRM 2007;58:8-18 (7) Spencer R.G.S. et al. JMR, 2000;142:120-135 (8) Bottomley P.A. 2009 In: Ency. Mag. Res., eds Harris R.K. and Wasylishen R.E.*