Reduced myocardial creatine kinase reaction rates in human heart failure: first measurements at 3T

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Introduction: Saturation transfer (ST) ^{31}P MRS techniques enable the in-vivo study of creatine kinase (CK) reaction kinetics. In muscle, the CK reaction is a putative shuttle, transporting high-energy phosphate between the mitochondria, where ATP is created, to the myofibrils, where it is used. The pseudo-first-order rate constant for CK (k_f) indexes the rate of generation of ATP from phosphocreatine (PCr). ^{31}P ST MRS using a Four Angle Saturation Transfer (FAST) protocol at 1.5T showed significant reductions in cardiac k_f in patients with heart failure (HF), suggesting that impaired CK energy supply may be specific for, and play a role in the contractile dysfunction and development of HF [1,2].

Recently, a Triple Repetition time ST (*TRiST*) protocol was introduced to efficiently measure k_f in the human heart at 3T [3]. In *TRiST*, the longitudinal relaxation time (T_1') and the equilibrium magnetization (M_0') of PCr are measured using the dual-repetition time (*TR*) method [4] with a short (cardiac-gated, 2 heart beats) and a long (10s) *TR* while the exchanging γ-ATP resonance at -2.5ppm is frequency-selectively saturated [3]. A third acquisition at a *TR* of 16s is then performed to measure the M_0 of PCr while applying saturation at +2.5ppm to control for spill-over irradiation. The rate is given by: $k_f^{TRiST}=1/T_1'(1-M_0'/M_0)$, where primes denote measurements recorded with γ-ATP saturated.

In this work, the *TRiST* method was applied to measure cardiac k_f in patients with HF for the first time at 3T.

Additionally, the intrinsic T_1 that would result in the absence of any exchange, $T_1^{intrinsic}=T_1'(M_0/M_0')$, as well as the T_1' of PCr, are also compared in patients and normal subjects. If $T_1^{intrinsic}$ is unchanged and/or is known in different patient groups, and because $k_f=1/T_1^{intrinsic}(M_0/M_0'-1)$, then k_f can be determined from just two fully-relaxed measurements of M_0 and M_0'. The result allows shortening the *TRiST* protocol to a more efficient, two repetition time ST method, *TwiST*.

Methods: *TRiST* data were acquired on a 3T Achieva Philips scanner in healthy subjects (5 men, 4 women, mean age of 29±10 years) with no history of hypertension, diabetes, or heart disease; and in HF patients (8 men, 8 women, mean age of 47±15 years) with New York Heart Association (NYHA) Class I or greater symptoms, a left ventricular ejection fraction ≤40%, and no significant coronary disease. 1-dimensional chemical shift imaging was used for localization with 17cm transmit and 8cm receive coils [4]. Data from slices covering the heart and the chest were averaged separately for each subject and the significance of differences determined by unpaired (between patient groups) and paired (k_f^{TRiST} vs k_f^{TwiST} in the same subjects) t-testing.

Results: k_f^{TRiST}, T_1', $T_1^{intrinsic}$, and k_f^{TwiST} acquired from the chest and the heart of normal subjects and patients with heart failure are shown in Table 1. k_f and T_1' in the heart are significantly reduced in heart failure patients as compared to normal subjects, in agreement with prior FAST studies at 1.5T [1,2]. $T_1^{intrinsic}$ is significantly different between the chest and heart, but differences between normal subjects and patients do not rise to statistical significance ($p<0.05$). Assuming average cardiac and chest $T_1^{intrinsic}$ values of 7.21s and 5.28s, respectively, in all subjects yields the same values of k_f^{TwiST} as k_f^{TRiST}.

		k_f^{TRiST} (s^{-1})	T_1' (s)	$T_1^{intrinsic}$ (s)	k_f^{TwiST} (s^{-1})	k_f^{FAST} (s^{-1})
chest	Normal	0.22±0.03†	2.51±0.20	5.48±0.64†	0.23±0.05†	0.22±0.07†
	Heart failure	0.18±0.05*	2.93±0.56*	5.17±2.38†	0.22±0.06**	0.21±0.08
heart	Normal	0.32±0.08	2.34±0.56	7.69±1.48	0.34±0.09	0.32±0.07
	Heart failure	0.21±0.10*	3.38±1.22*	6.94±1.53	0.20±0.07*	0.21±0.07*

Table 1: Mean±SD of k_f^{TRiST}, T_1', $T_1^{intrinsic}$, and k_f^{TwiST} acquired in the chest and the heart of normal subjects and patients with heart failure compared to k_f^{FAST} from [1] acquired at 1.5T. * $p<0.05$ vs. normal; ** $p<0.05$ vs. k_f^{TRiST}; † $p<0.05$ vs. heart.

Discussion: These first 3T measurements of cardiac CK kinetics in patients with heart failure show significant reductions in k_f, in close agreement with prior results obtained at 1.5T using a different method (k_f^{FAST} in Table 1) [1,2]. These data obtained with a different technique at a different field strength further demonstrate reduced CK energy supply in the failing human heart. The intrinsic $T_1^{intrinsic}$ showed no significant differences between normal subjects and patients allowed the *TriST* method to be shortened by one acquisition to the *TwiST* protocol, without significantly changing k_f. However, prior knowledge of $T_1^{intrinsic}$ is still required, and the sensitivity of measurements of $T_1^{intrinsic}$ to the particular frequency-selective saturation method needs further work.

References: (1) Weiss RG *et al*, PNAS 2005; 102: 808. (2) Smith CS *et al*, Circulation 2006; 114: 1151. (3) Schär M *et al*, ISMRM 2009; 17: 709. (4) El-Sharkawy AM *et al*, Magn Reson Med 2009; 61: 785.

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