Post-contrast myocardial T1 is more sensitive and precise than partition coefficient/ECV to cardiovascular disease: phantom and human validation

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Introduction: The T1 mapping technique in cardiovascular magnetic resonance (CMR) allows detection of diffuse myocardial fibrosis in a wide range of conditions including cardiomyopathy, hypertrophic cardiomyopathy and amyloidosis. To measure the T1 time, a gadolinium contrast agent is typically administered, followed by measurement of T1 time by CMR at one or more time intervals.

Pre/post contrast myocardial T1 values (1,2), partition coefficient (λ) and extracellular volume fraction (ECV) (3) have all been proposed as measures of discrimination for cardiac disease. In particular, these measures allow identification of diffuse myocardial fibrosis. Recent guidelines seem to favor the use of ECV (4) over other T1 mapping measures of diffuse fibrosis. In addition, earlier works have looked at the precision of T1 mapping techniques (5,6) by studying the effect of noise on T1 values. However, there is scant theoretical and experimental evidence to date favoring one of the T1 mapping measures for CMR over the other. In this work, we systematically compare the accuracy and sensitivity of T1 mapping measures.

Materials and Methods: ECV is calculated from pre- and post-contrast R1 (=1/T1) values in myocardium (m) and blood (b) using

$$ECV = f = \lambda \,.\, [1-Hct] = (R1_{cm} - R1_{pm}) / (R1_{cb} - R1_{pb}) \quad [1]$$

λ is the partition coefficient and [Hct] refers to the hematocrit, $R1_{cm}$ is the relaxivity of post-contrast myocardium, $R1_{pm}$ that of pre-contrast myocardium; $R1_{cb}$ is the relaxivity of post-contrast blood while $R1_{pb}$ is relaxivity of pre-contrast blood.

Errors in each term in Eq. 1 then propagate as

$$\sigma_{ECV} = [\sigma^2_{R1pm} .(\partial f / \partial R1_{pm})^2 + \sigma^2_{R1cm} .(\partial f / \partial R1_{cm})^2 + \sigma^2_{R1pb} .(\partial f / \partial R1_{pb})^2 + \sigma^2_{R1cb} .(\partial f / \partial R1_{cb})^2 + \sigma^2_{Hct} .(\partial f / \partial [Hct])^2]^{1/2} \quad [2]$$

assuming each term varies independently without bias.

Clearly, as long as $T1_{cm}$ (=1/$R1_{cm}$) value is not biased, precision should be higher for this measure than for the derived ECV value. The problem arises when this value is biased, typically due to acquisition scheme and heart rate variation. In addition, post-contrast myocardial T1 ($T1_{cm}$) also varies with dose, time after contrast and GFR. Correction for variation due to dose, time and GFR (7) as well as heart rate can be effected.

A) MRI experiments: A phantom consisting of four tubes with DTPA $NiCl_2$-agar solutions mimicking pre/post contrast myocardium and blood was imaged on a Philips 3T Achieva scanner using a 5-3 MOLLI sequence with following relevant scan parameters: TI_{min}/TI_{max} = 146/400ms, TFE factor=79, TR/TE = 2.5/0.9ms, α = 35°. The heart rate was varied from 50 bpm to 100 bpm with six repeated T1 measurements at each HR. The experiment was repeated on a second Philips 3T scanner. The COV (σ/μ) of $T1_{cm}$ obtained prior to and after HR correction and compared with COV of λ (or ECV since [Hct] is irrelevant for a phantom) was used as a surrogate for precision. Monte Carlo simulations were also performed using measured μ and σ of T1 values to derive σ for ECV using Eq. 2.

B) Human Study: Higher accuracy should result in better power to identify disease. To test this, 9 healthy and 17 patients (age and sex matched) with heart failure (HF) underwent cardiac MRI after administration of 0.15mmol/kg of gadopentetate dimeglumine. Pre/post-contrast T1 mapping was done using the MOLLI sequence. T1 values in myocardium and blood pool were used to determine λ and at two post-contrast time points — 12 min and 25 min. Similar to the phantom experiment, COV at each time point in each group (healthy or HF) and for each of the three measures was determined as a surrogate for accuracy. Student's t-test for the three measures between healthy and HF subjects for each time point served as a marker of sensitivity. In addition, COV and t-test were also performed on T1 values obtained at time = (12, 25) min which were corrected to time = (25, 12) min for both normals and HF subjects using a previously described analytical model (7).

Results: Table 1 shows COV from the phantom experiment. Using HR corrected values, Monte Carlo simulations provided a COV of 0.0378 which matched value calculated from eqn. 1 (0.0376). In human studies, the mean COV for the post-contrast T1, λ and ECV at the two time points was 0.0896, 0.0962 and 0.1158 for normal subjects; COV was 0.0935, 0.1091 and 0.103 for HF. A lower value of COV reflects better homogeneity in the two separate populations (healthy and HF) which indirectly reflects on the precision of the three measures. Student's t-test between normal and HF subjects resulted in mean p-values (one tailed) of 0.0211, 0.0551 and 0.0883 for post-contrast T1, λ and ECV, indicating better sensitivity of post-contrast T1 values. Despite employing a previously described analytical correction for time, mean COV for post-contrast T1 values (healthy and HF) was 0.0917 while p-value was 0.023.

TABLE 1	Before HR correction		After HR correction	
	$T1_{cm}$	ECV	$T1_{cm}$	ECV
Scanner 1	0.0346	0.0151	0.005	0.008
Scanner 2	0.0294	0.0164	0.0056	0.0077
Combined	0.0325	0.0154	0.0059	0.0158

Table 1: Coefficient of variation (COV) for $T1_{cm}$ and ECV obtained from phantom measurements

Discussion: We have shown that post-contrast myocardial T1 time is a relatively more ***precise and sensitive*** marker of CVD compared with λ and ECV. Any systematic bias in post-contrast T1 value due to HR, GFR, time and dose can be corrected for in a straightforward manner under certain conditions. HR correction is less effective at longer T1 times resulting in an even greater penalty for ECV calculations. Additional scanning and post-processing to derive pre-contrast T1 values as well as co-registration with post-contrast T1 maps to derive ECV can also be eschewed.

References: [1] L. Iles et al. *JACC* 2008;52(19):1574. [2] C. Sibley et al. *Radiology* 2012;265(3):724. [3] P.Kellman et al. *JCVMR* 2012;14:63. [4] J. Moon et al. JCVMR 2013; 15:92. [5] N. Gai et al. *Procs ISMRM*, 2010:4986. [6] P. Kellman et al. *JCVMR* 2013; 15:56. [7] N. Gai et al. *MRM* 2011; 65:1407.