Tau$_i$, A Metabolic Imaging Biomarker for Myocardium

William D Rooney[1], Craig S Broberg[2], and Charles S Springer, Jr.[1]

[1]*Advanced Imaging Research Center, Oregon Health & Science University, Portland, Oregon, United States,* [2]*Division of Cardiovascular Medicine, Oregon Health & Science University, Portland, Oregon, United States*

Introduction: Contrast-enhanced ^1H_2O T_1-weighted cardiovascular MRI measurements find wide use (1). Almost all are interpreted using tracer paradigm [TP] expressions; *e.g.*, the extra-/intra-vascular partition coefficient of the paramagnetic Gd(III) chelate contrast agent [CA; which plays the tracer role] (2). Built-in to any TP formulation, however, is the limitation that tracer molecule compartmentalization is not intrinsic to its signal. Though correct for true tracers, this is incorrect for ^1H_2O T_1 data: the signal molecule is water, not CA (3). Use of TP to analyze such data assumes the mean intracellular water molecule lifetime (τ_i) is effectively zero. However, in 2006, perfused heart NMR experiments revealed that τ_i is not zero but near or over 200 ms (4). In order to account for this, one must employ expressions from the shutter-speed paradigm [SSP] (3). Failure to do so leads to significant consequences. Here, we show these for the human heart.

Methods: We acquired serial ^1H_2O T_1-weighted data at 1.5T from 4 normal human subjects before and after a single bolus IV injection of 0.15 mmol/kg of CA (Omniscan). Quantitative T_1 measurements were made using a Look-Locker technique [non-selective inversion, 21 inversion times] for a single 8 mm slice located in the mid-ventricular short axis plane. The tissue ROI comprised ~300 voxels [nominally, (2x2x8) mm^3; 32 μL] located in the left ventricular wall. The blood ROI comprised ~25 voxels in the left ventricle. Hematocrit values were obtained to estimate plasma T_1.

Results: **Figure 1** plots ROI ^1H_2O myocardial tissue (R_{1t}) *vs.* corresponding blood plasma (R_{1p}) values [$R_1 \equiv T_1^{-1}$] during the bolus passage for one subject. There are three post-CA points, and one pre-CA. Rigorous SSP recognizes there are three general compartments ["sites"] between which water molecules exchange: blood, interstitium, and intracellular (3). However, the Fig. 1 data points can be fitted with an approximate shutter-speed [SS′] two-site-exchange [2SX] expression truly appropriate for only perfused *ex vivo* hearts (4,5), cell suspensions (6), or tissue with a tight blood-tissue-barrier (7). Use of 2SX in myocardium assumes a *varying* CA extravasation steady-state, $[CA_o] = [CA_p]$ (o, interstitial, "outside"); the solid curve. Here, the curve returns extracellular volume fraction ECV(SS′) [$\equiv v_e$(SS′)] = 0.33 and τ_i = 410 ms. The TP predicts a straight line for the R_{1p}-dependence of R_{1t}, with slope v_e. We have plotted this as the dashed line. The experimental data are not linear. In order to be fitted to the data, the TP straight line must be pivoted down about their origin. If we do this, we obtain ECV(TP) = 0.19, a 41% reduction from ECV(SS′). Note that SS success is mostly not a matter of fitting goodness. Putting the straight line through the data points incurs residuals not much larger than for the 2SX curve. The importance lies in the systematic depression by the TP of the ECV, which is generally increased in pathology (1,8,9). Thus, SS correction for TP distortion of ECV is crucial. However, τ_i is completely inaccessible to the TP. From our fitting, we obtain τ_i = 410 ms for the human myocardium. As far as we are aware, this is the first human myocardial τ_i value reported. The **Table** gives the population-averaged [n = 4] parameter values.

ECV (TP)	0.19 (±0.01)
ECV (SS′)	0.31 (±0.04)
τ_i	0.31 (±0.09) s

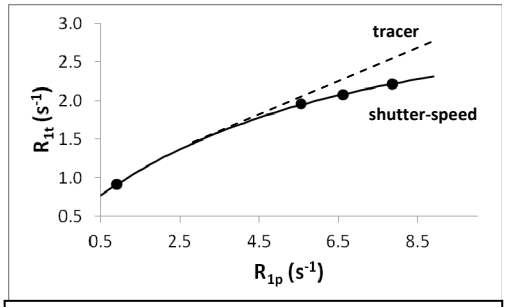

Figure 1. SSP′ fitting of DCE-MRI data collected from normal human heart *in vivo*. The circles represent data at four times: one pre-CA, and three post-CA. R_{1t} is the myocardial tissue ^1H_2O R_1 value, and R_{1p} is the blood plasma ^1H_2O R_1 value calculated for a (micro) hematocrit [Hct] of 0.33. The solid curve represents the best SS′ model fitting [ECV(SS′) = 0.33; τ_i = 0.41 s] of the data. The dashed line is the tracer expectation for ECV = 0.33.

Discussion: An important consequence is that the crucial myocardial ECV parameter is underestimated by TP in proportion to its magnitude (3,8,9). However, since $[CA_o] > [CA_p]$ (10), the 2SX approximation used here [and in (8,9)] overestimates ECV in inverse proportion to its magnitude (3,10). Only the rigorous SSP (3,6) will approach the true ECV. We estimate that, for a conservatively large CA transfer constant K^{trans} = 0.4 min^{-1}, ECV(SS) = 0.25, and τ_i = 220 ms.

Even more important, however, is that inter-compartmental water exchange kinetics are not accessible by the TP: water is not recognized as molecular but assumed a space-filling continuum. The τ_i [the equilibrium water efflux rate constant (k_{io}) reciprocal] value is assumed → 0 in TP. For a cylindrical myocyte of diameter d: $\tau_i^{-1} = 4(P_W/d)$, where P_W is the cytolemmal water permeability coefficient (6). For a 20 μm d value: τ_i^{-1} = 2000 P_W (τ_i in s, P_W in cm/s). For a P_W of 5 x 10^{-4} cm/s: τ_i^{-1} = 20 d^{-1} (d in μm). Thus, τ_i^{-1} is linearly related to P_W and linearly related to d^{-1}, with different coefficients. However, the P_W factor dominates (6,9). For control mice τ_i = 190 ms, and for a hypertensive mouse model τ_i = 440 ms, values have been reported (9). Note the very large (132%) τ_i increase in the compromised mouse heart. However, the accompanying d value [from *ex vivo*, fixed tissue] increased from 19.8 to 26.2 μm, *i.e.*, by only 32%. Most importantly of all, P_W itself is dominated by an active trans-membrane water cycling process (6). The first hint of τ_i metabolic sensitivity came in the perfused *ex vivo* rat heart study (4), finding that (no flow) ischemia increased τ_i by 52% - from 184 to 280 ms. These results are consistent with τ_i dominance by the P_W factor, and its sensitivity to metabolic activity slowing caused by both ischemia and the induction of hypertension. The τ_i magnitude is sensitive to the ATP_i and K_o^+ substrates of, and to specific inhibitors of, of the driving ATPase transporters (5,6). Thus, τ_i^{-1} is proportional to the activity of the driving cytolemmal ATPase ion pump; Na^+/K^+ATPase in the heart. The smaller the τ_i, the greater the activity.

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