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Tau_i, A high-resolution metabolic imaging biomarker for myocardium

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Background

Contrast-enhanced ^1H_2O T_1-weighted cardiovascular MRI is usually interpreted using tracer paradigms; e.g., the extra-/intravascular contrast agent (CA) partition coefficient. However, the signal molecule is water, not CA. Consequently, the myocardial extracellular volume fraction (ECV) is underestimated in proportion to its magnitude. Even more importantly, intercompartmental water exchange kinetics are inaccessible. The mean intracellular water molecule lifetime [tau_i] is assumed effectively 0; though it is a fraction of a second. For cylindrical myocytes with mean cytolemmal water permeability coefficient P_W and diameter d: $tau_i^{-1} = 4(P_W/d)$. tau_i^{-1} is linearly related to P_W and to d^{-1}. However, P_W dominates and is itself dominated by active trans-membrane water cycling. Thus, tau_i^{-1} is proportional to the driving cytolemmal ATPase ion pump activity.

Methods

We acquired serial 1.5T T_1-weighted ^1H_2O data from 6 normal human subjects before and after a single bolus 0.15 mmol/kg CA IV injection. The tissue and blood ROIs comprised ~300 LV wall and ~25 LV voxels [(2 × 2 × 8) mm^3]. Hematocrit values allowed R_{1p} estimation.

Results

Figure 1 plots ROI ^1H_2O LV wall tissue (R_{1t}) vs. corresponding LV plasma (R_{1p}) values during the bolus passage [$R_1 \equiv T_1^{-1}$]: 3 post-CA points and 1 pre-CA, for one subject. These are fitted with a shutter-speed (SS) two-site-exchange [2SX] expression approximating CA extravasation steady-state, $[CA_o] = [CA_p]$ (o, interstitial); the solid curve [only v_e and tau_i varied]. The extracellular volume fraction $v_e(SS)$ [≡ ECV(SS)] is 0.38. The tracer paradigm (TP) predicts a straight line for the R_{1t} R_{1p}-dependence, with slope v_e: the dashed asymptote. In order to fit the non-linear data, the TP straight line must be pivoted down about the origin: this yields ECV (TP) = 0.25, a 34% reduction. SS success is not a fitting goodness issue: the TP line through the data incurs residuals scarcely larger than for the 2SX curve. Crucial is the systematic TP ECV depression, which increases in pathology. Even more important is the SS access to tau_i - because of the active trans membrane water cycling link to metabolic activity. We obtain tau_i = 0.34 s for this subject, the first reported for human myocardium [means in Table 1]. (Since $[CA_o] > [CA_p]$, v_e and tau_i are over- and underestimated.) Pixel by-pixel v_e and tau_i values allow parametric mapping.

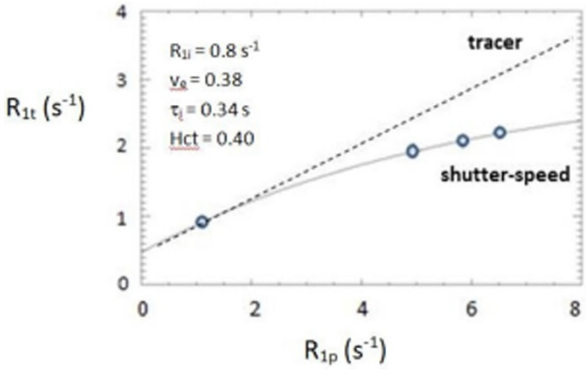

Figure 1 SSP fitting of DCE-MRI data collected from normal human heart in vivo. The points represent data collected at four times: one prior to CA administration, and three post-CA administration. R_{1t} is the myocardial tissue ^1H_2O R_1 value, and R_{1p} is the blood plasma ^1H_2O R_1 value calculated for a hematocrit (Hct) of 0.4. The solid curve represents the best SS model fitting to the data with parameters shown in the inset. The dashed asymptotic line is expected for the tracer paradigm.

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Table 1 [n = 6]

ECV(TP)	0.26 (+/- 0.02)
ECV(SS)	0.33 (+/- 0.04)
tau_i	0.20 (+/- 0.09) s

Conclusions

The first tau_i metabolic sensitivity hint came in a 2006 perfused ex vivo rat heart study (with other collaborators) finding that (no flow) ischemia increased tau_i by 56% - from 0.18 to 0.28 s. For control mice tau_i = 0.19 s, and for a hypertensive mouse model tau_i = 0.44 s, values have been reported. The very large (132%) tau_i increase is accompanied by an only 30% d increase; from 20 to 26 μm. These results demonstrate P_W dominance of tau_i, and sensitivity to metabolic activity slowing caused by both ischemia and chronic hypertension.

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