The impact of water exchange on dynamic contrast enhanced MRI: can we estimate tissue water residence times in vivo?

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Introduction Tracer kinetic modeling of dynamic contrast enhanced MRI (DCE-MRI) can provide estimates of hemodynamic parameters such as perfusion and blood volume which are of interest in oncology. Because the tracer is monitored indirectly via its effects in the surrounding water molecules, the exchange of water between tissue compartments can affect modeled parameter estimates [1]. The importance of water exchange (WX) effects for analysis of data acquired using clinical protocols is uncertain [2,3], however, previous work has shown that DCE data acquired using a 30° flip angle is not sufficiently sensitive to measure water residence times [2], and it is known that WX effects are more important at lower flip angles [3]. In this study, a dual-flip angle acquisition with two injections of contrast agent was designed to answer two questions: Is there a measurable difference in WX sensitivity between low and conventional flip angle acquisitions? And does a dual bolus dual flip angle acquisition contain sufficient information to allow measurement of tissue water residence times? The parotid was chosen for testing this protocol in volunteers because of its favorable DCE MRI characteristics - good extravasation, and a measurable extravascular extracellular space (EES), v_e, and plasma volume, v_p [4].

Methods The parotid glands of 7 volunteers aged 21 to 59 were imaged on a 1.5 T Philips Intera scanner using a SENSE 18 element neurovascular coil. An ECG-gated Q-flow phase contrast sequence was used to acquire 75 flow measurements in the ascending aorta over one cardiac cycle to enable measurements of cardiac output, using a flip angle/TR/TE of 10°/5.4/3.2 *ms*, 1.25x1.25x8 *mm* reconstructed voxels, SENSE factor of 2, venc 200 *cm/s*.

Five multi-shot inversion recovery TFE (IR-TFE) sequences were run to acquire data for a pre-contrast T_1 map. These sequences had a flip angle/shot interval/TR/TE 12°/4000/2.8/1.01 *ms*, SENSE factor of 3, FOV of 180x180 *mm*, 176x147 matrix, 1.02x1.02 mm reconstructed voxels, 25x3 *mm* slices, inversion times of 80, 250, 1000, 2500, 3900 *ms*.

Three series of 3D T_1-weighted spoiled fast field echo (FFE) acquisitions were run with flip angles of 30°, 5°, and 30°, TR/TE 2.94/1.07 *ms*, SENSE factor of 3, and the same geometry as for the IR-TFE. Ten dynamic volumes were acquired at 30° (for S_0 calculation), followed by 230 volumes at 5°, and 230 volumes at 30° with a temporal resolution of 2.2 s. 0.05 *mmol/kg* Gd-DOTA (Dotarem; Guerbet, Aulnay-sous-Bois, France) was injected using a power injector at 3 *mL/s* during the acquisition of the 10th volume of each of the long series.

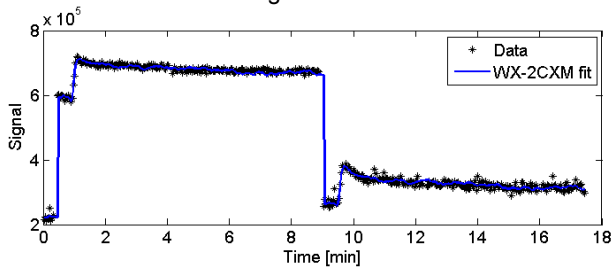

Fig 1 A typical signal-time curve in the parotid gland fitted with the WX-2CXM. The 5° data were acquired first, followed by the 30° data.

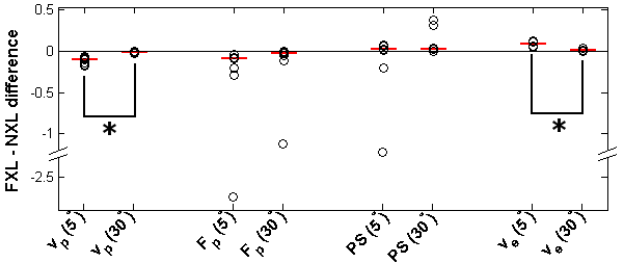

Fig 2 The difference between FXL and NXL parameter estimates is shown for the parameters v_p, F_p, PS, and v_e. The 5° data show a significantly greater FXL-NXL difference (*) than the 30° data for both v_p and v_e.

Analysis Parotid glands were outlined on post-contrast images and small regions were defined in a distal slice of the internal carotid for arterial input function (AIF) estimation. AIFs were corrected using the measured cardiac output [5], which was calculated by integrating the area under the flow curve over one cardiac cycle using the Q-flow data. A 6-parameter model including WX effects (WX-2CXM, [1]), was fitted to the full signal timecourse and estimates of water residence times in the vascular, intracellular, and EES pools (τ_v, τ_{ic}, τ_e) were obtained. A relaxivity of 3.6 /mM/s, haematocrit of 0.42, and T_1 values from IR-TFE were used to calculation tracer concentration from signal. Boundary conditions of the WX-2CXM, the 4 parameter fast (FXL) and no exchange (NXL) limit models [1], were each fitted to the 5° and 30° portions of the timecourse separately. Estimates of plasma perfusion (F_p), v_p, v_e, and the capillary permeability surface area product (PS) were obtained using all 3 models.

Results The 5° portion of the timecourse demonstrated a significantly greater separation between the FXL and NXL estimates of v_e and v_p than the 30° portion (Fig 2, $p<0.05$, Mann Whitney test), confirming increased WX sensitivity in the 5° timecourse. Sufficient WX effects were present in the data to fit the full 6 parameter WX-2CXM, and median parameter estimates are given in table 1. Good fits of the WX-2CXM to the full timecourse were seen for all 7 datasets (e.g. Fig 1).

Discussion and Conclusions The DCE timecourse provided sufficient WX sensitivity to provide preliminary estimates of water residence times, indicating that water in the parotid spends proportionally more time in the intracellular space than in the EES or vascular space; however, these estimates show a large variance and validation is required. The 5° portion of the timecourse was more sensitive to WX than the 30° portion as shown by the separation of the FXL and NXL fits in fig 2; WX effects were particularly significant for v_e and v_p. This protocol was tested in the parotid gland, but in the future this sequence could be applied in other tissues where tissue water residence times are of interest, particularly tumors.

parameter	median	range
F_p (ml/min/ml)	0.47	0.13-0.79
v_p	0.20	0.10-0.29
PS (ml/min/ml)	0.05	0.004-0.11
v_e	0.14	0.001-0.30
τ_v (s)	0.10	~0-2.5
τ_{ic} (s)	0.55	0.03-24
τ_e (s)	0.05	~0-0.54

Table 1 Mean WX-2CXM parameter estimates for 2CXM parameters v_p, F_p, PS, and v_e, and water residence times τ_v, τ_{ic}, and τ_e.

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