Optimization of 19F MR quantification of administrated PFC nanoparticle in vivo: mathematical simulation and experimental validation

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Introduction: Perfluorocarbon (PFC) nanoparticle (NP) presents a great potential as molecular MR contrast agent. The unique 19F MR signature of PFC NP has been widely exploited for conducting quantitative MRI because of practically no background signal from physiological tissue [1]. However, the spin-lattice relaxation (T1) of PFC emulsion is inversely correlated with oxygen concentration which varies in different tissues (e.g., in tumor and artery); therefore, it is necessary to choose proper in vivo acquisition parameters to minimize the oxygenation effect on quantitative 19F MR determined regional concentration of PFC NP. Additionally, acquisition parameters should be optimized to maximize the SNR, a general concern for in vivo 19F MR applications. In this study, the effect of TR and TE on the accuracy of quantitative 19F MR were estimated with mathematical simulation followed by in vivo validation.

Materials and Methods: *Simulation:* Based on Bloch equation, simulations of spin echo spectroscopy sequence were preformed in Matlab (Mathworks, Inc.). First, the expected 19F signal intensity as a function of TR and TE was simulated to assess the SNR. Subsequently, two simulations were conducted by setting 19F T1 relaxation time of PFC NP to 0.9 s, simulating normoxia condition (21% [O2]), and 0.6 s, simulating hyperoxia condition (100% [O2]) [2]. The calculated oxygenation induced quantification error was plotted as a function of TR and TE. T2 of all simulations were set to be 0.3 s. Percentage difference of quantifications between normoxia and hyperoxia scenario is defined as $(S_{hyperoxia}-S_{normoxia})/S_{normoxia}$. *In vivo 19F MRI/S:* MR experiments were performed on 11.7 T Varian INOVA MR System. Three C57BL/6 mice incubated under room air were intravenously injected with 20% v/v perfluoro-15-crown-5-ether NP emulsion (4 mL/Kg) through the tail vein. At three-hour post injection, mice were anesthetized with a standard dose of ketamine/xylazine. A solenoid 19F coil was placed on the right rear leg of mice. A 1H scout image of the leg was first acquired to visualize the anatomy. Subsequently, a T1-weighted spin-echo 19F image (TR = 350 ms, TE = 16 ms) was acquired to visually examine the 19F signal intensity, followed by 19F T1 measurement using an inversion recovery spin-echo sequence (TR = 5 s, TI increases from 5 ms to 1.8 s with 0.2 s interval). Finally, quantification of regional PFC NP concentration was conducted with previously reported 19F MR spin-echo spectroscopic method (TR = 0.3, 2.0, and 3.0 s) by using trifluoroacetic acid (TFA) sealed in pipette tip as reference standard [1]. Two sets of images were acquired for each mouse when it was breathing room air (normoxia condition) or 100% oxygen (hyperoxia condition). Other parameters for 19F imaging were: RF excitation bandwidth, 350 Hz; number of average, 128; in plane resolution: 1mm * 1mm; slice thickness: whole projection.

Results: Fig. 1 shows the simulation result. The optimal parameter for achieving the highest SNR is TR≈1.5*T1 (Fig. 1A). Additionally, the quantification difference between normaxia and hyperoxia was less than 5% when TR ≥ 3 *T1 (Fig. 1B). Fig. 2 shows in vivo 19F MR result of mouse leg after PFC NP treatment. T1-weighted 19F signal in mouse leg under normoxia was apparently lower than that under hyperoxia (Fig. 2B & C). Correspondingly, a ~50% decrease of 19F T1 was observed from nomoxia to hyperoxia (Fig. 2D). Because of the oxygenation effect on 19F T1, a more than 100% quantification error of PFC NP concentration was observed when TR = 0.3 s. However, the quantification error was insignificant when TR = 3 s, i.e. ≥ 3*T1 (Fig. 2E).

Discussion and conclusion: We demonstrated that in vivo 19F MR determined PFC NP concentration is *not* sensitive to tissue oxygenation when TR ≥ 3* T1 at 11.7T. Results from mathematical simulation were in agreement with that of in vivo experiment. Thus, long TR (over 3 times T1) should be used in in vivo studies to guarantee 19F MR determined PFC quantity will accurately reflect the 19F spin-density.

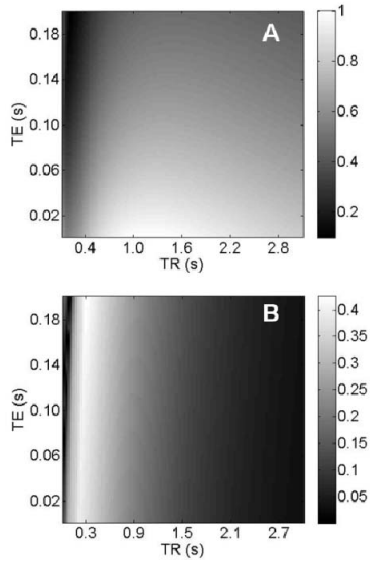

Figure 1. (A) The normalized SNR of 19F MRI as a function of TR and TE in a fixed time frame. T1 is set to be 0.9 s. (B) The percentage difference of the simulated 19F signal intensity for T1=0.9s and 0.6 s .

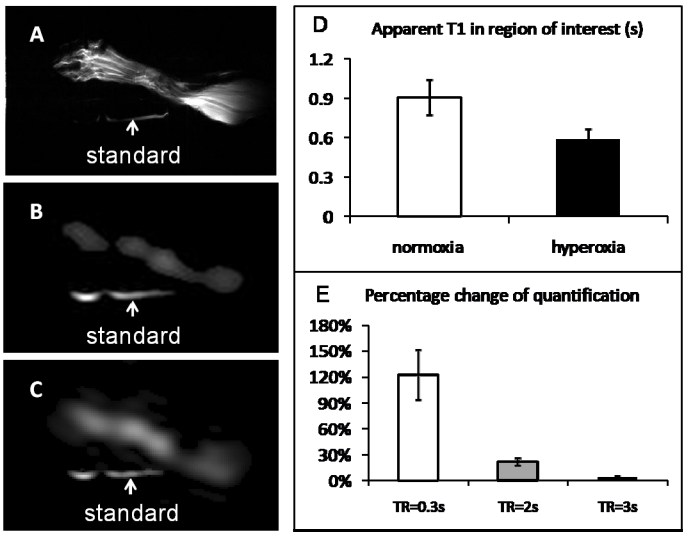

Figure 2. (A) High resolution 1H image shows the position of the mouse leg and a TFA standard (arrow). (B-C) T1 weighted 19F image of mouse leg when the animal was under normoxia (B) or hyperoxia (C). (D) 19F T1 of PFC NP in mouse leg under normoxia and hyperoxia. (E) Quantification difference (in percentage) of PFC NP using different TR.

References: [1] Richard Southworth, el at., Nanomedicine 5:359-367, 2009; [2] Anne M. Neubauer, et al., Magn Reson Med 60:1066-1072, 2008.