Translating pH-sensitive PROgressive saturation for Quantifying Exchange using Saturation Times (PRO-QUEST) MRI to a 3T Clinical Scanner

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Synopsis

In this work, a recently developed method called PRO-QUEST (PROgressive saturation for Quantifying Exchange using Saturation Times) is translated to a 3T clinical scanner for assessing pH-sensitive indices in phantoms and a healthy volunteer. Our results demonstrate that quantification of pH sensitive indices using PRO-QUEST is feasible at 3T within clinically acceptable acquisition times. Our initial findings suggest that PRO-QUEST has the potential to provide a new biomarker to study neurological disorders associated with brain tissue acidosis.

Introduction

Understanding pH regulation in the brain is important both in healthy and pathophysiological conditions because tissue acidity may be a key characteristic associated with neurological disorders such as schizophrenia, bipolar disorder, panic attack and ischemia[1-3]. Recently, the feasibility of mapping pH sensitive exchange rates was demonstrated in phantoms and *in vivo* ischemic rat brains using a novel pulse sequence called PRO-QUEST (PROgressive saturation for Quantifying Exchange using Saturation Times)[4]. We aimed to translate PRO-QUEST to a 3T clinical scanner and estimate pH-sensitive indices for phantoms with various pH values and a healthy volunteer.

Methods

The PRO-QUEST sequence was implemented on a 3T Philips Ingenia MRI scanner (Philips Healthcare, Best, the Netherlands) and tested on phantoms consisting of 100mM glutamate in a standard solution of 1x phosphate-buffered saline (PBS) with several pH (6.08, 6.64 and 7.19) and a pure PBS sample (pH 7.14). Phantoms and a healthy volunteer were scanned using a 32 channel head coil. First, a Look-Locker (LL) sequence (Figure 1a) was implemented with 20ms delay times (in lieu of off-resonance saturation pulses displayed in Figure 1b) prior to a multishot turbo field echo planar imaging (TFEPI) readout (EPI factor=7) and n acquisitions (n=128 for phantom; n=143 for volunteer) with the following imaging parameters: imaging pulse=sinc-gaussian, duration=0.67 ms, flip angle=8°\15°, TE=3.8 ms, time between readout pulses=42 ms, acquired resolution=1.88x2.14x5 mm^3 (phantom) and 1.96x2.04x5mm^3 (volunteer), TR=6s. For the PRO-QUEST scans (Figure 1b), an off-resonance saturation pulse centred at 3.0ppm (glutamate phantom) or 3.5ppm (volunteer) was applied prior to the TFEPI readouts with identical imaging parameters as the LL sequence. Parameters for the off-resonance saturation pulses used in the PRO-QUEST sequence are as follows: off-resonance saturation pulse=sinc-gaussian, bandwidth=300Hz, duration=20 ms, flip angle=400° (equivalent of 1.3µT). For the healthy volunteer scan, single slice acquisitions were obtained with a scan time of 2 min 6 s (3 averages) per sequence. Imaging parameters are summarised in Table 1. Additionally, standard multi-echo turbo spin echo (TSE) sequence (TSE factor=20) consisting of 10 echoes with TE=20-200ms with 20ms of inter-echo spacing was used to quantify T_2 (to be used as a input parameter in equation 2) in the same geometry as PRO-QUEST.

Data processing was performed using custom-written scripts in MATLAB (The Mathworks, Natick, MA, USA). The derived Block-McConnell models[4] were fitted to magnitude data using maximum likelihood estimation. The following equation was fitted to LL data to estimate the equilibrium magnetization M_0, T_1 and B_1:

$$M_{zd}(n\tau)=\{1-[(\cos\theta)^{n-1}e^{-(n-1)\tau R_1}]\}M_{zd}(\tau)/\{1-[(\cos\theta)e^{-\tau R_1}]\}+M_0(1-e^{-t_d R_1})[(\cos\theta)^{n-1}e^{-(n-1)\tau R_1} \text{ -----[1]}$$

where $M_{zd}(\tau) = M_0 (1-e^{-\tau R_1})$; t_d is the time between the initial saturation pulse and the first readout pulse; τ is the time between readout pulses with small flip angle θ; $R_1 = 1/T_1$; n is number of acquisitions.

Next, the obtained M_0,T_1, B_1 values were used as input parameters for estimating the exchange-dependent relaxation, R_{ex} by fitting the PRO-QUEST data:

$$M_{zsat}(n\tau)=\{1-[(\cos\theta)^n e^{-n(\tau R_1-t_{sat}(R_1-R_{1\rho}))}]\}M_{zsat}(\tau)/\{1-[(\cos\theta)e^{-(\tau R_1-t_{sat}(R_1-R_{1\rho}))}]\}+M_0(1-e^{-t_d R_1})[(\cos\theta)^n e^{-n(-\tau R_1-t_{sat}(R_1-R_{1\rho}))}] \text{ -----[2]}$$

where $M_{zsat}(\tau) = M_{ss} (1-e^{-(R_{1\rho}t_{sat})})(\cos\theta)e^{-(\tau - t_{sat})R_1} + M_0(1-e^{-(\tau-t_{sat})R_1}$; $M_{ss} = (R_1\cos^2\phi)/R_{1\rho}$; $R_{1\rho} = R_1\cos^2\phi+(R_2+ R_{ex})\sin^2\phi$; ϕ is the angle between the effective field and the z-axis. Further definition of the equations and parameters are described in literature[4].

Results and Discussion

Similar to the pre-clinical cases[4], progressive saturation recovery curves with off-resonance saturation pulses show clear separation among samples with various pH values in glutamate and PBS (Figure 2b) while the ones without off-resonance saturation pulses are nearly indistinguishable (Figure 2a). The estimated R_{ex} significantly correlates with pH in glutamate samples (Figure 2c). In the healthy volunteer, the PRO-QUEST image of signal evolution at the final phase of the amide proton resonance shows clear contrast between white and grey matters (WM/GM) (figure 3b) as contrary to the LL image (without off-resonance saturation pulses) (figure 3a). The origin of contrast between WM and GM needs further investigation. As for prerequisite parameters in estimation of PRO-QUEST indices, calculated T_1 values from the LL scan in a healthy volunteer are remarkably consistent with literature values (table 2)[5-7]. The pH sensitive R_{ex} shows differences between WM and GM.

Due to intrinsic limitations of the specific absorption rate and duty cycle (50%) at clinical field strength, the efficiency of the off-resonance saturation scheme is somewhat compromised. Nonetheless, clinical translation of this technique is very feasible given its easy implementation on standard clinical platforms and the use of existing LL-type of readouts, therefore not requiring pulse programming. Further work is required to achieve full brain coverage within clinically relevant acquisition time.

Conclusion

Our results demonstrate that quantification of pH sensitive indices using PRO-QUEST is feasible at 3T within clinical acquisition time. Our initial findings suggest that it would be worthwhile to apply PRO-QUEST for studies on patients with neurological impairment associated with acidosis to better understand its distinct imaging features relative to conventional techniques.

Acknowledgements

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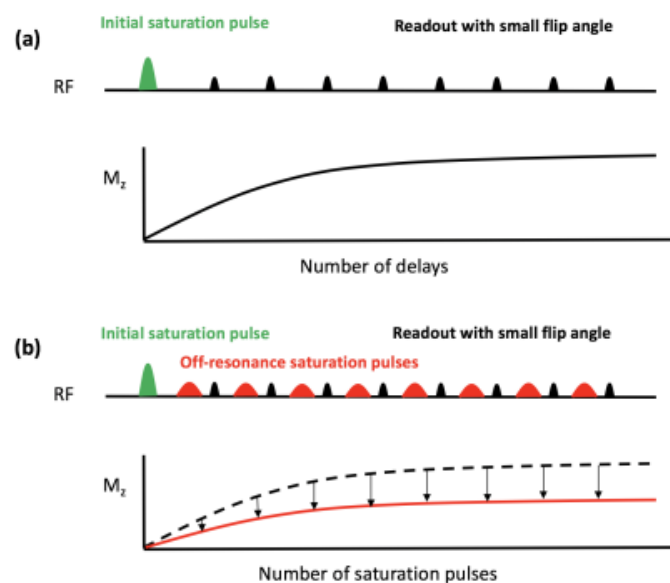
Figures

Figure1. A simplified diagram of the pulse sequence. First, an initial saturation pulse is employed to achieve effective nulling of the longitudinal water magnetisation. Then, (a) delays (LL scan) or (b) off-resonance saturation pulses (PRO-QUEST scan) are applied and interleaved with the acquisition of segmented exchange-weighted images. Progressive saturation gives rise to an observable signal reduction in M_z throughout relaxation.
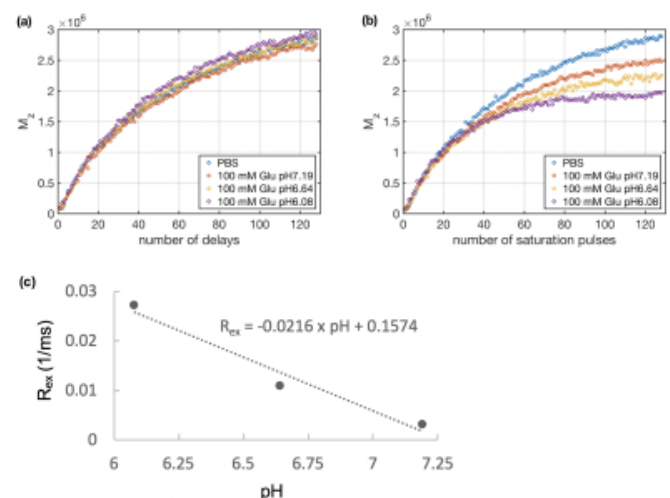

Figure 2. Saturation recovery curves of (a) LL scan (with delay) and (b) PRO-QUEST scan (with off-resonance saturation pulses) in PBS and glutamate

(Glu) samples (100mM) at pH=6.08, 6.64 and 7.19. (c) Correlation between R_{ex} and pH in glutamate samples (100mM).
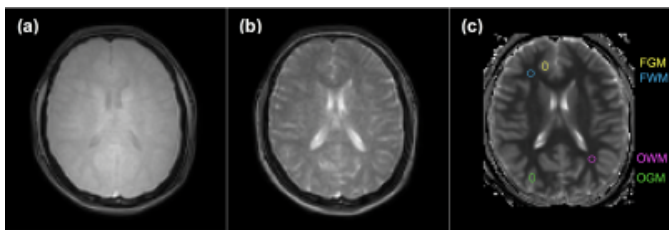

Figure 3. Axial brain images of steady-state saturation recovery curves (at the final phase) using (a) LL scan (with delay) and (b) PRO-QUEST scan (with off-resonance saturation pulses) in a healthy volunteer. (c) T_1 map for which raw data were obtained from two LL sequences with small flip angles of 8° and 15°, was computed by maximum likelihood estimation.

	Acquired resolution (mm²)	Number of slices	TR (ms)	TE (ms)	Number of acquisitions	t_s (ms)	τ (ms)	Offset frequency (ppm)	Number of averages	Scan time for each LL or PQ scan (min:sec)
Phantom	1.88x2.14x5	3	6000	3.8	128	29.7	42.1	3	1	2:30
Healthy volunteer	1.96x2.04x5	1	6000	3.8	143	29.7	41.9	3.5	3	2:06

Table 1. Imaging parameters utilised in this study. Note that offset frequency is applied to only PRO-QUEST (PQ) scan among 3 scans: 1st LL scan [8° readout pulse x number of acquisitions], 2nd LL scan [15° readout pulse x number of acquisitions] and PQ scan [(off-resonance pulse + LL with 8° readout pulse) x number of acquisitions].

	T_1 (ms)				R_{ex} (1/ms)
	Present Study	Study[5]	Study[6]	Study[7]	
FWM	884 ± 10	838 ± 18	847 ± 43	699 ± 38	0.1475 ± 0.0052
OWM	908 ± 17	832 ± 18		758 ± 49	0.1323 ± 0.0077
FGM	1264 ± 38	1322 ± 34	1763 ± 60	1209 ± 109	0.0518 ± 0.0066
OGM	1371 ± 31	1283 ± 37		1122 ±117	0.0463 ± 0.0047

Table 2. T_1 relaxation times of the present study as compared to literature and R_{ex} values from the present study. ROIs are displayed in Figure 3c. FWM = frontal white matter; OWM = occipital white matter; FGM = frontal grey matter; OGM = occipital grey matter.