In vitro CEST-based pH in muscle (patho)physiological range at 3T

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INTRODUCTION:

Muscle pH has demonstrated to be a valuable biomarker in neuromuscular diseases and its standard measurement is based on MRS approaches [1]. However, as (total)creatine (tCr)-CEST is an application that is inherently sensitive to pH, it can be used to obtain pH maps noninvasively, with a spatial resolution close to quantitative MRI-based maps such as water T2 and water T1 maps in muscle [2,3]. tCr CEST applications on 3T clinical scanners are challenging due to the low frequency shift between tCr and water, and the restrained pH range in neuromuscular disorders. Here, we report the optimization work of tCr-CEST-based pH maps at 3T in phantoms in a narrow range of (patho)physiologically realistic pH values.

METHODS:

An aqueous phantom (set 1) consisting of 7 vials at different pH values between pH=6.00 and 8.00 was prepared for the calibration of the AREXratio method and another aqueous phantom (set 2) was prepared with 6 vials at different pH values in the physiological range to evaluate the sensitivity and the reproducibility. All pH values were controlled with a pH-meter. Experiments were performed using a 3T clinical scanner Magnetom Prisma^{FIT} (Siemens Healthineers, Erlangen, Germany) and a 15-channel transceiver RF coil.

A pulsed CEST-FLASH sequence was acquired at 41 frequency offsets regularly spaced between -4ppm and 4ppm, centered on the water frequency. The saturation pulse train was directly optimized *in vitro* by varying the duration of pulses, the total saturation duration, the duty cycle and the B1 value. A 3500ms long saturation pulse train composed by a series of 99ms rectangular saturation pulses with a 1ms inter-pulse delay (duty cycle=99%) was run twice, with two different B1 values: 1.0µT and 1.5µT. The parameters of the FLASH readout were: matrix size = 128x128, FoV = 180x180mm, slice thickness = 9mm, TR = 7.4ms, TE = 3.9ms, FA = 10°, bandwidth = 520Hz, 1 excitation. WASAB1 images were collected for B0 and B1 corrections and were reconstructed with an open-sources Matlab (Mathworks,Natick, USA) algorithm [4,5]. All other steps were carried out with in-house Python code, including z-spectrum denoising based on Singular Value Decomposition (7 components were kept with soft thresholding).

Experiments were repeated five times to calibrate the AREXratio (AREXratio vs pH, set 1) and three times to assess the measurements reproducibility in the realistic pH range (set 2). The position of the vials was changed between each acquisition.

RESULTS:

The AREX-ratio value correlated linearly with the true pH (pH-meter values) between pH=6.7 and 7.5 (R^2 = 0.99, y = -0.37x + 3.33, Fig 1.**A.**), which correspond to the *in vivo* pH range. CEST-based pH shows a strong correlation with pH measured by pH-meter in the (patho)physiological range (R^2=0.98) and reproducibility was high over the three experiments (Fig 1.**B.**). Denoising highly decreased the standard deviation in the vials (Fig 1.**C.**) without losing sensitivity to small pH variations.

DISCUSSION AND CONCLUSION:

We demonstrated the sensitivity and the reproducibility of CEST-based pH mapping to physiological pH values in the range of 6.9-7.3 *in vitro* at 3T, which is in good agreement with the work of Rerich et al. performed on a 7T scanner. These results are promising in the light of *in vivo* applications to study pH variations in skeletal muscles.

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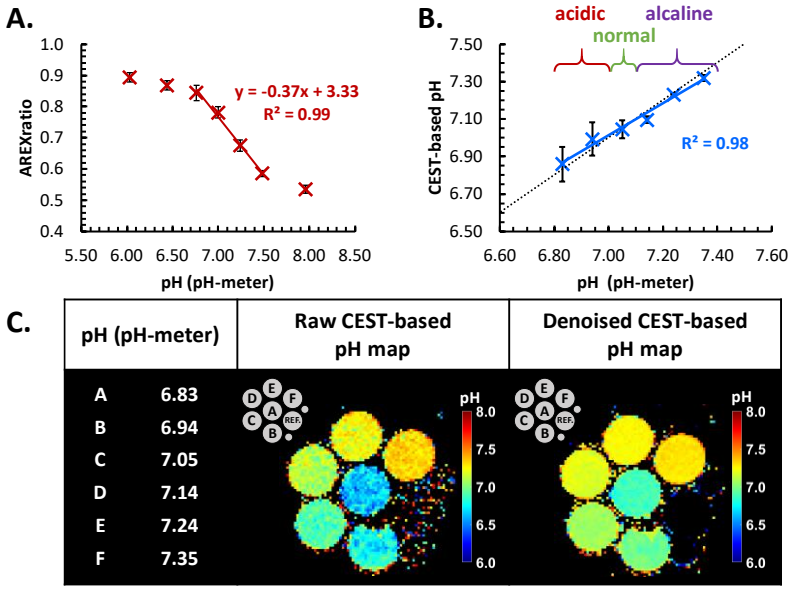

Fig 1. **A.** Calibration curve which correlate AREXratio with pH measured by pH-meter. **B.** Correlation between CEST-based pH after denoising and pH measured by pH-meter. The black dotted line corresponds to the identity line. **C.** Comparison between CEST-based pH map before and after denoising.