Quantitative sodium breast MRI: a pilot study for estimating (pseudo) intracellular sodium concentration and (pseudo) extracellular volume fraction in vivo

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Target audience. Those interested in breast cancer screening and imaging.

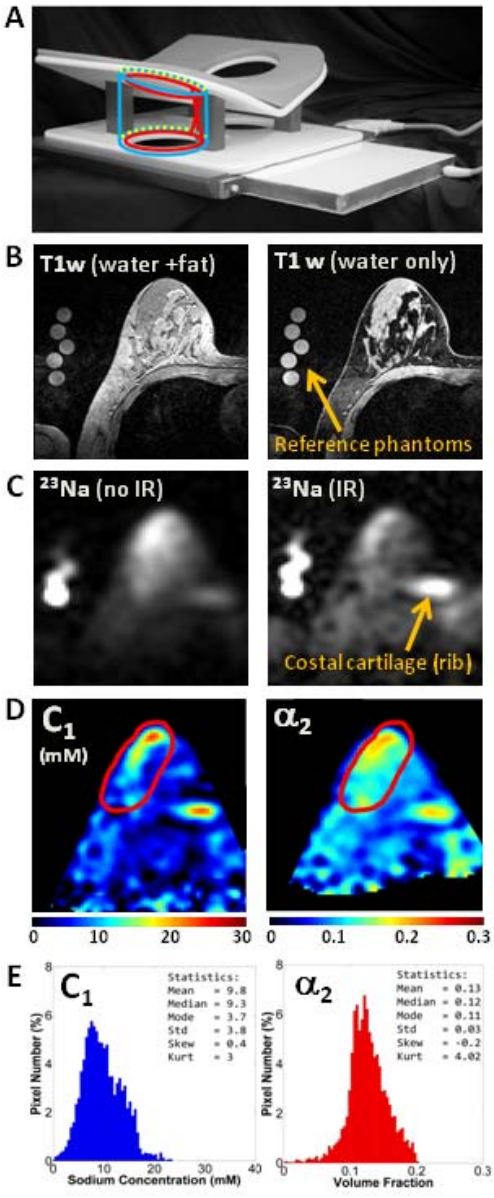
Purpose. False-positive breast cancer diagnoses from standard imaging techniques such as mammography and ^{1}H dynamic contrast enhanced MRI result in significant overdiagnosis, unnecessary biopsy, and overtreatment [1]. Sodium (^{23}Na) MRI allows a quantitative assessment of biochemical information in tissues, such as cell viability or ion homeostasis, which could provide a new reliable means to assess breast tumor malignancy and grade [2-5]. Tumor malignancy can be characterized by cell proliferation, which is associated with altered Na^+/K^+-ATPase activity leading to increased intracellular sodium concentration (C_1) [6], and by tumor neovascularization and increased interstitial space resulting in increased extracellular volume fraction (α_2) [7]. In this pilot study, we implemented a non-invasive ^{23}Na MRI method [8] to quantify (pseudo) C_1 and α_2 in vivo with the goal of improving breast cancer screening.

Methods. MRI: Data was acquired with a prototype dual-tuned RF coil on a 3T Tim Trio scanner (Siemens, Erlangen, Germany). Three healthy female volunteers (age 28±5 years) were scanned after informed written consent was obtained in accordance with our local IRB. **^{1}H**: Two T1-weighted 3D GRE acquisitions were performed for localization: one with water+fat excitation and one with water excitation only, resolution = 1×1×1.5 mm^3, TA = 3:15 min. **^{23}Na**: Two acquisitions allowed C_1 and α_2 to be calculated: one in which total sodium is detected and a second in which extracellular and fluid sodium is suppressed (or within noise level of the image) by inversion recovery (IR). Data were acquired with the FLORET [9] sequence with TR = 100 ms, TE = 0.2 ms, 3 hubs of 110 interleaves, 6.25 mm base resolution, 22 (no IR) and 34 averages (IR), TI = 24 ms (for IR), TA = 12:06 (no IR) and 18:42 (IR). Images were reconstructed offline in Matlab using regridding with a nominal isotropic resolution of 3.125 mm. Sodium concentration was calculated by performing linear regression on ^{23}Na signal maps in the breast (pre-corrected to account for heterogeneous coil sensitivities) with respect to signal levels in reference phantoms with known ^{23}Na concentrations (10, 30, 50, 70 and 100 mM). Pseudo C_1 and α_2 maps were then generated by assuming a 3-compartment model that includes solid, intracellular, and extracellular spaces [8]. **RF coil prototype:** The primary coil is a dual-tuned solenoid, active in both transmit and receive modes at both ^{23}Na and ^{1}H frequencies. The solenoid contains two loops: a posterior loop near the chest wall and an anterior loop surrounding the breast apex (red overlay in Fig. 1A). The secondary coil is a single-tuned (^{23}Na) receive-only loop whose main axis is in the left/right direction perpendicular to the solenoid (solid blue overlay in Fig. 1A). To reduce radiation loss in the ^{1}H solenoid, the ^{23}Na receive loop is connected to a conductive segment (blue-yellow overlay in Fig. 1A) that is interspersed with ^{23}Na trap circuits, creating a partial shield around the ^{1}H solenoid.

Results. Results are shown in Fig. 1B-E (from one volunteer). Fig. 1F shows the mean±standard deviation (std) of the results in three subjects. In summary, mean C_1=9.2±0.5 mM and mean α_2=0.15±0.06 are in the expected range of values for healthy tissues in vivo [**2**]. Kurtosis (kurt) and skewness (skew) of the distributions are also presented and are close to values of a Gaussian distribution (skew = 0, kurt = 3).

Discussion/Conclusion. Quantitative sodium MRI is feasible in the breast at 3T with a prototype coil. Pseudo C_1 and α_2 values in healthy human tissue were well-matched to those in the literature, providing proof of concept of the proposed technique [2,3,7]. Previously reported correlation between tumor malignancy and measured parameters C_1 and α_2 suggests that the method can be expected to distinguish healthy and cancerous tissue. The term 'pseudo' represents experimental uncertainties arising from low ^{23}Na SNR, partial volume effects, inter-compartmental T_1 variation, imperfect inversion pulse, etc. The measured C_1 and α_2 values might therefore include signal from both adjacent voxels and adjacent compartments within a voxel. While absolute measures of C_1 and α_2 are preferred, pseudo C_1 and α_2 values will be sufficient to achieve the long-term goal of detecting changes between healthy and cancerous breast tissues. To improve ^{23}Na SNR and alleviate errors arising from partial volume effects related to the coarse 6.25 mm base resolution used in these measurements, we are developing a many-element RF coil and an optimized ^{23}Na protocol that exploits denoising and compressed sensing, which are harmonious with the inherently oversampled FLORET data. We believe the proposed quantitative ^{23}Na method could supplement standard clinical ^{1}H MRI and mammography to significantly improve the specificity of breast cancer screening, thereby reducing overdiagnosis and overtreatment.

References. [**1**] Esserman LJ, JAMA 310(8), 797-798, 2013. [**2**] Madelin G, JMRI 38, 511-529, 2013. [**3**] Boada FE, Curr Top Dev Biol 70, 77-101, 2005. [**4**] Ouwerkerk R, Breast Cancer Res Treat 106(2), 151-160, 2007. [**5**] Kaggie JD, MRM 71(6), 2231-2242, 2014.[**6**] Cameron IL, Cancer Res 40(5), 1493-1500, 1980. [**7**] Sykova E, Prog Brain Res 125, 155-178, 2000. [**8**] Madelin G, Sci Rep 4, 4763, 2014. [**9**] Pipe JG, MRM 66(5), 1303-1311, 2011.



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	C_1		α_2	
	Mean	Std	Mean	Std
Mean	**9.2**	0.5	**0.15**	0.06
Std	**4.3**	0.3	**0.04**	0.01
Skew	**0.6**	0.2	**-0.4**	0.1
Kurt	**3.0**	0.1	**3.2**	0.7

Figure 1. A. ^{1}H/^{23}Na RF coil prototype. **B.** ^{1}H MRI. **C.** ^{23}Na MRI. **D.** C_1 and α_2 maps. **E.** C_1 and α_2 distributions (within the red ROI in D). **F.** Table of mean and std of mean, std, skewness (skew) and kurtosis (kurt) of the C_1 and α_2 distributions in breast over 3 healthy subjects.