Quantitative ^{31}P Magnetic Resonance Spectroscopy of the breast at 7 Tesla.

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Introduction:
^{31}P Magnetic Resonance Spectroscopy is a non-invasive tool capable of assessing the free phosphorylated metabolites (phosphomonoesters (PME) and phosphodiesters (PDE)), which may be used in the evaluation of anti-cancer treatment, as shown in preclinical studies [1,2]. Since the concentration of PME and PDE in the glandular tissue is very low, their ^{31}P MR signals will be low and can be contaminated by signal contributions from highly concentrated phosphorylated compounds of the chest muscle. With an optimized coil design for ^{31}P MRS of the breast and a magnetic field strength of 7 Tesla the signal to noise ratio can be significantly increased. Outer volume suppression may be applied to minimize signal contamination from muscle tissue while maximizing the detection volume. In addition, using image based registration to determine sensitivity information from glandular tissue, ^{31}P MRS of the breast may be obtained in a quantitative manner.

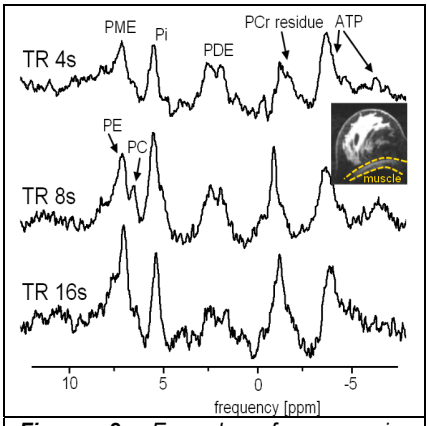

Figure 2: *Example of progressive saturation series of the breast (inset figure). Adiabatic excitation with saturation slab on the muscle.*

Aim: To obtain quantitative measures for phosphorylated metabolites in the human breast at 7 Tesla.
We determined the concentration and the T1 relaxation time of the phosphocholine (PC) and phosphoethanolamine (PE) of only glandular tissue in young healthy volunteers.

MRS methods:
Eleven healthy women were examined (age 25 ± 3y). A two-channel double tuned unilateral RF coil was designed for ^{31}P and ^{1}H MRI and MRS of the human breast and interfaced to a whole body 7T MR system (Philips, Cleveland, USA). A fast-field-gradient-echo (FFE) sequence was used to image the breast tissue (T1- weighted, selective water excitation, fat-suppressed, flip angle 10°, TR 8.8ms, TE 2.3ms). Shimming with 2nd order shim gradients was based on a manually segmented region of interest in the breast from a B_0 map. ^{31}P MR spectra were obtained from the entire breast using pulse acquired FID with an adiabatic excitation (90° BIR-4 pulse, duration 8 ms, limited bandwidth of 1800 Hz). To eliminate contributions of ^{31}P MR signal from breast muscle tissue (recognized by the presence of phosphocreatine (PCr), which concentrations are undetectable in breast tissue) one saturation slab was used before excitation (Fig. 1). To reach optimal suppression of the signals from the muscle, the power of the spatially localized saturation pulse was manually adjusted for every volunteer. A progressive saturation series was used to determine ^{31}P T1, TR was set to 4, 8 and 16 seconds, number of averages was adapted to maintain equal acquisition time of 8:32 minutes (Fig. 2). Single Gaussian lines were fitted to the data with AMARES, JMRUI 3.0.

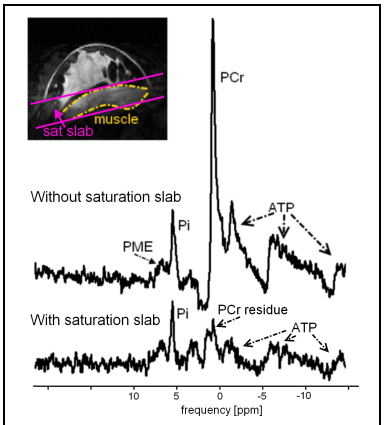

Figure 1: *^{31}P MR spectra of the breast (inset figure) without (upper) and with (bottom) the saturation slab. PCr and ATP resonances are significantly suppressed without effecting the resonances of (PME) and Pi that originate from glandular tissue.*

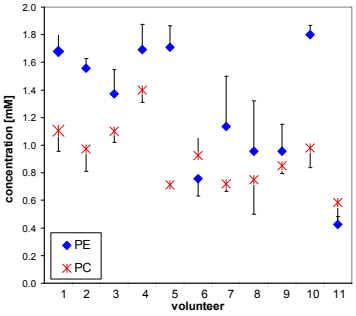

Figure 3: *Calculated concentration of PE and PC in 11 healthy volunteers. (corrected for 15% loading difference between phantom and volunteer)*

Quantification based on MR imaging and phantom calibration:
The area under the fitted *in vivo* peaks of PE and PC were scaled to the area under the curve of PE and PC in a calibration phantom with known concentration. We corrected the obtained concentrations for differences of glandular tissue volume, for B_1 inhomogeniety of the ^{31}P coil, and for T1 relaxation of ^{31}P spins. Since we efficiently suppressed signals from the muscle, we assumed that all ^{31}P signal originated from glandular tissue. The amount of glandular tissue was determined from the FFE images using homebuilt software for tissue segmentation. A ^{31}P 3D image of a phantom that fitted the entire coil was used to obtain a sensitivity map of the ^{31}P coil (90° BIR-4 pulse, TR 20s, scan matrix 4x4x8, acq time 9hrs). The ^{31}P-sensitivity map was matched and multiplied with a mask of the glandular tissue, which was obtained from the segmented FFE images (Fig.4). The same was done for the ^{31}P sensitivity image and the FFE image of the calibration phantom. The ratio between the total intensity of the new ^{31}P image (Fig. 4 bottom right) of the glandular tissue and the calibration phantom was used to correct for volume and B_1 inhomogeniety. Finally, a pickup-probe was used to correct for loading differences between phantom and *in vivo* experiments.

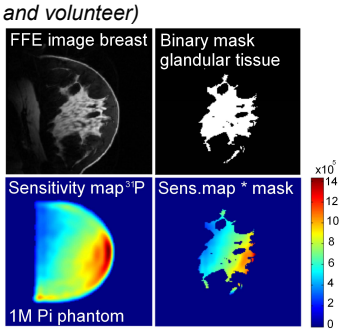

Figure 4*: Procedure for quantification based on ^{31}P and ^{1}H imaging.*

Results and Discussion:
Signals from muscle tissue were sufficiently suppressed to attribute the origin of the remaining ^{31}P signals of PME and PDE to glandular tissue. The signals from PE, PC and inorganic phosphate were detected in all volunteers with sufficient SNR and spectral resolution for reliable fitting. The amount of suppression of ^{31}P signals from muscle tissue was limited by the non uniformity of the B1 field of the ^{31}P coil. However, the muscle tissue was typically far away from the coil and thus contributing less to the received signal. If some PCr residue signal was present, this was, apart from strongly reduced, often out of phase and shifted due to the saturation and different B_0 fields in the muscle. Due to superb lipid suppression in the MRI, simple threshold segmentation could be applied. Loading differences between subject and phantom resulted in 15% signal reduction respectively. Quantitative numbers for PE and PC were calculated and summarized in table 1 and figure 3. The error bars on the values in figure 3 represent the standard deviation of the concentrations determined in each of the three MR spectra per volunteer.

Table 1: Quantification, n=11	PE	PC
T1 relaxation [s]	5.7 +/- 0.9	4.4 +/-1.0
average concentration [mM]	1.29 +/- 0.45	0.92 +/- 0.23

Conclusion:
We were able to detect and quantify PC and PE in the breast of healthy volunteers. Using a dedicated ^{31}P breast coil at 7T combined with outer volume suppression, the PME signals had good SNR and were artifact free. With routine proton imaging and phantom calibration measurements the PME content could be quantified to absolute concentrations. These concentration found for PE and PC are within physiological range and agree with literature that report on total choline (=PC+GPC+choline) levels in the breast [3]. Therefore, we have shown that quantitative ^{31}P MRS of the breast is feasible and enables detailed studies of breast cancer that may contribute to improved diagnosis and monitoring of anticancer therapy.

References: [1] Aboagye, Bhujwalla. Cancer research 1999;59(1) [2] Podo NMR Biomed 1999;12(7) [3] Bolan, Meisamy, MRM 2003;50(6)