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Adding a new spectral dimension to localized ^{1}H MR spectroscopy of human prostates using an endorectal coil [1]

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Abstract. Localized 2D shift-correlated MR spectra (L-COSY) of human prostates were recorded using an endorectal "receive" coil. Typically, 4 ml voxels were placed in the peripheral zones of the prostate. Seven healthy volunteers and one BPH patient have participated in this study so far. The total acquisition time for a 2D L-COSY was approximately 20 minutes. A 1.5 Tesla GE scanner with a body coil for RF transmission and a pelvic phased-array coil combined with a disposable rectal coil for reception was used. The 2D L-COSY spectra showed cross peaks due to citrate, spermine and occasionally choline, creatine and lipids. The 2D cross peaks due to both the multiplets of spermine were clearly resolved from choline and creatine which has been a major problem with the conventional MR spectroscopic techniques. In contrast to 2D JPRESS, improved spectral dispersion, less crowded 2D cross peaks and unequivocal detection of both multiplets of spermine were monitored in 2D L-COSY. Pilot results suggest that localized 2D L-COSY can be successfully implemented in human prostates on a clinical scanner.

Keywords: Prostate, spermine, citrate, 2D L-COSY, endorectal

1. Introduction

Prostate cancer is one of the most common causes of death from cancer among men worldwide [1]. The treatment options are determined by the clinical staging of the carcinoma; hence, preoperative staging of prostate carcinoma (PCa) is a critical component of patient management. Intracapsular (stage B) carcinoma is normally treated by radical prostatectomy; however, patients with known extension of the tumor into the lymph nodes, seminal vesicles or periprostatic fat (stage C or D) generally receive internal or external radiation therapy (as prostatectomy would be insufficient to eradicate those tumors) [2]. Magnetic resonance imaging (MRI) with an endorectal surface coil has allowed clear visualization of the prostatic capsule and neurovascular bundle, thereby facilitating the detection of stage C disease [3]. However, the specificity of MRI alone is limited due to factors other than cancer, including post-biopsy hemorrhage, prostatitis and therapy that can alter the images of the peripheral zone used as an indicator of cancer [1,2]. Therefore, magnetic resonance spectroscopy (MRS), allowing noninvasive measurements of the relative concentrations of prostate metabolites, has been explored as a complementary tool for prostate tissue diagnosis and cancer staging [4–8].

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Studies of one-dimensional MRS have found a number of notable characteristics distinguishing prostate malignancies from healthy prostates. Using a transrectal ^{31}P MRS probe, Thomas and coworkers found malignant prostates to have significantly decreased levels of phosphocreatine (PCr) and increased levels of phosphomonoesters (PMEs) as compared to healthy prostates [9]. Proton MRS studies using an integrated endorectal pelvic phased array coil have found consistently reduced levels of citrate (Cit) (measured in relation to choline (Ch) and creatine (Cr), as $\mathrm{Cit}/(\mathrm{Ch}+\mathrm{Cr})$) in PCa compared with benign prostatic hyperplasia (BPH) and the peripheral zone (PZ) of the normal prostate [10].

In one-dimensional MRS, the analysis of the polyamines such as putrescine, spermidine and spermine is hindered by the overlap of their spectral peaks with the resonances of choline, creatine, other metabolites, and fat. However, two-dimensional (2D) spectroscopy allows the separation of many otherwise overlapping peaks, due to the added second spectral dimension [11,12]. Recently, Yue et al. implemented a 2D JPRESS spectroscopic sequence in PCa and BPH patients, and the results were compared to that of healthy controls [13]. The resulting spectra showed the peaks due to polyamines well resolved from the overlapping Cr and Ch resonances [11,13]. Polyamines were significantly decreased in PCa, and citrate was increased, in BPH. These findings were in agreement with a recent *ex vivo* MRS and high performance liquid chromatography (HPLC) study [14].

The protons of spermine resonate at two locations, one at 3.1 ppm and the second at 2.1 ppm as two triplets. Due to the off-resonance effect of the last 180° rf pulse that resolves the J-coupled multiplets along the second dimension, the multiplet at 2.1 ppm was not recorded reliably in 2D JPRESS [13]. The 2D localized correlated spectroscopy (L-COSY) technique gives improved spectral dispersion in the second axis compared to 2D JPRESS [15]. Therefore, when applied to the prostate, 2D L-COSY is expected to yield a more definitive resolution of polyamines than 2D JPRESS. The goals of this project were to investigate the spectral dispersion of J-coupled metabolites in the human prostate, such as citrate, choline, creatine, spermine and lipids, using the 2D L-COSY sequence, and to test whether the cross peaks due to spermine can be resolved unambiguously from the overlapping choline and creatine peaks in the low field region and the lipid peaks in the high field region.

2. Materials and methods

2.1. Human subjects

Seven healthy volunteers (mean age of 39 years) and one BPH patient (64 years) have participated in this study so far. Informed consent was obtained from each subject in keeping with the institutional review board (IRB) guidelines.

2.2. Phantoms

Four phantoms containing solutions of 10 mM citrate, 10 mM spermine, 10 mM creatine and 10 mM choline were prepared in 250 ml plastic bottles and the pH was controlled at 7.2.

2.3. MRS acquisition parameters

The voxel localization was done in one shot by a new MRS volume localization sequence called CABINET (coherence transfer based spin-echo spectroscopy). The CABINET sequence had a combination of three slice-selective rf pulses (90°–180°–90°) to localize a desired voxel. The last 90° rf pulse also acted

as a coherence transfer pulse for 2D L-COSY [15]. Global water suppression was achieved by a CHESS sequence prior to voxel localization [16].

The MRS voxel of interest (VOI) was prescribed using an axial fast spin-echo MRI using the following parameters: 4 mm thick slices with 1.5 mm spacing, TR/TE = 2.5 s/84 ms, FOV = 14–24 cm, data matrix size = 256 × 192, 4 NEX and a total duration of 4 minutes. The 2D L-COSY spectra were recorded using the following parameters: TR = 2 s, minimal TE = 30 ms, 40–64 t_1 increments and 12–20 averages each. The total acquisition time was 16–34 minutes. The raw data were acquired using 1024 complex points and a spectral window along the first dimension of 2500 Hz. The incremental period (Δt_1) was 1.6 ms to yield a spectral window of 625 Hz along the second dimension. Typical voxel sizes were 2–12 ml, localized in both peripheral and central zones.

A 1.5 T whole body MRI/MRS scanner (GE Medical Systems, Waukesha, WI) with a maximum gradient amplitude of 2.3 G/cm was used. A disposable endorectal probe combined with a pelvic phased-array coil (MEDRAD, Pittsburgh, PA) was used for signal reception and a body rf coil for transmission. For the phantom study, a body coil and a 3-inch surface coil (GE Medical Systems, Milwaukee, WI) were used for the RF transmission and MR signal reception, respectively.

2.4. Simulation

The 2D COSY spectra of four prostate metabolites were simulated using a computer program, GAMMA (general approach to magnetic resonance mathematical analysis) [17]. The first 90° rf pulse of the L-COSY sequence used for simulation consisted of a binomial rf pulse ($1\overline{3}3\overline{1}$) to mimic water suppression [18,19]. The numerals give the relative pulse lengths, the bars indicate a 180° phase shifted pulse and equal delays between pulses are set. Thus $1\overline{3}3\overline{1}$ corresponds to $11.25°(x) - t - 33.75°(-x) - t - 33.75°(x) - t - 11.25°(-x)$, $t = 1/2\Delta f$, and Δf is the offset frequency [18]. The phase shift was optimized based on the target, a null at the water frequency. The parameters used for simulation were identical to that of experiments.

2.5. MRS post-processing

Only the signal from the endorectal coil was used for further processing due to its superior signal strength compared to that of the pelvic phased-array receivers. The raw spectral files were transferred to an SGI O2 workstation (Silicon Graphics Inc., Sunnyvale, CA) with IRIX 6.5. A FELIX software package (Accelrys, San Diego, CA) was used for post-processing. The raw MRS data matrix was apodized with skewed squared sinebell filters along the two axes and the experimental data matrix was zero-filled to 2048 × 128. The simulated data matrix was zero-filled to 2048 × 256. After a double Fourier transformation, the L-COSY spectra were reconstructed in the magnitude mode and the resulting 2D spectra were displayed as contour plots.

3. Results and discussion

The 2D L-COSY spectra of four major metabolites that have been identified in human prostate, namely citrate, creatine, choline and spermine were recorded using a 1.5 T MRI scanner; each 2D spectrum was color-coded differently, and the spectra were overlaid on top of each other. The 2D cross peaks due to citrate (Cit) were close to each other and the diagonal as well. As explained previously [11,13,20], citrate has two identical methylene groups. The two protons of each methylene group form a strongly coupled

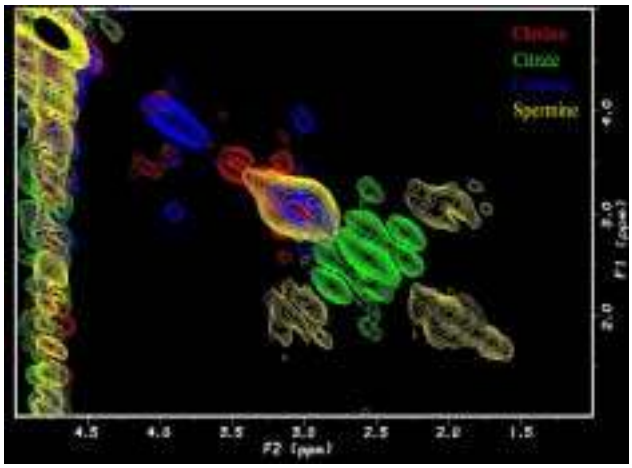


Fig. 1. The phantom spectra of four major prostate metabolites, namely citrate (10 mM), choline (10 mM), creatine (10 mM) and spermine (10 mM). The experimental 2D spectra were color-coded and superimposed on top of each other. (TR = 2 s, 1024 points in F_2 and 64 points in F_1 dimension).

AB spin system and the two doublets are separated by approximately 10 Hz with $J = 8$ Hz. Spermine (Spm) has two sets of methylene groups from which one triplet resonates at 3.1 ppm and the other at 2.1 ppm with $J = 8$ Hz. The cross peaks between these two multiplets were identified at ($F_2 = 3.1$ ppm, $F_1 = 2.1$ ppm) and ($F_2 = 2.1$ ppm, $F_1 = 3.1$ ppm). In agreement with our earlier report [15], the cross peaks of Cr were identified at ($F_2 = 3.0$ ppm, $F_1 = 3.9$ ppm) and ($F_2 = 3.9$ ppm, $F_1 = 3.0$ ppm). Choline consists of three methyl groups resonating at 3.15 ppm as a singlet and two methylene groups at 3.5 ppm and 4 ppm that are J-coupled. The 2D cross peaks between the two methylene groups were identified at ($F_2 = 4.0$ ppm, $F_1 = 3.5$ ppm) and ($F_2 = 3.5$ ppm, $F_1 = 4.0$ ppm) [15]. The 2D spectra of these individual metabolites were also simulated using a GAMMA library. Similar to Fig. 1, the resulting 2D spectra were color-coded differently and overlaid on top of each other as shown in Fig. 2. The experimental *in vitro* and simulated 2D spectra were in excellent agreement.

A typical 2D L-COSY spectrum of a 28 yo healthy human prostate along with the axial MRI is shown in Fig. 3. A $2 \times 2 \times 1$ cm^3 voxel was placed on the lower left peripheral zone as shown in Fig. 3(a). Excellent water suppression was achieved. The cross peaks due to spermine were well separated on both sides of the diagonal in agreement with the in vitro and simulated spectra as shown in Figs 1 and 2. The 2D peak volumes under the cross peaks of spermine at ($F_2 = 3.1$ ppm, $F_1 = 2.1$ ppm) and the diagonal peak of Cit were calculated to check the reliability of 2D L-COSY of healthy human prostates. The mean ratio of Spm/Cit ($n = 6$) was 0.11 ± 0.03 (SD), with a coefficient of variation (CV) of 24%, after excluding one spectrum due to technical difficulties.

An axial MRI of an enlarged prostate (BPH) and the corresponding 2D L-COSY spectrum are shown in Fig. 4. The placement of the $2 \times 2 \times 3$ cm^3 voxel is shown on the MRI (Fig. 4(a)). Comparing the healthy spectra with that of the BPH, we noted an increase in citrate but the change in spermine was not significant. Further research using a larger patient cohort is necessary.

Compared to 2D JPRESS, the endorectal 2D L-COSY of human prostates has an improved spectral dispersion (a broader spectral window along F_1) and the two multiplets of spermine were clearly assigned in 2D L-COSY using the two cross peaks above and below the diagonal. However, the resolution is not yet enough to separate spermine from spermidine and putrescine. It is known that putrescine (a precursor of spermine/spermidine) would also have a cross peak at 3.1 and 2.1 ppm [21]. Therefore

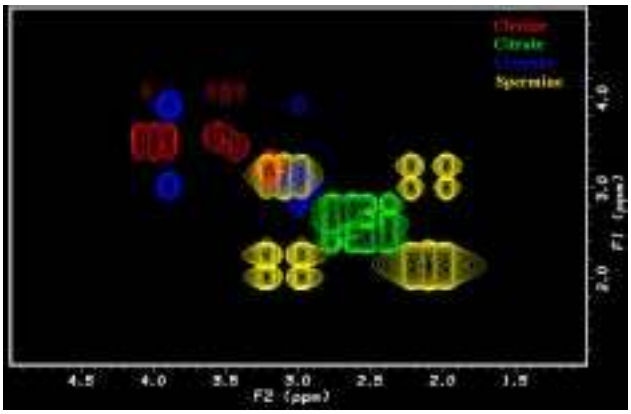
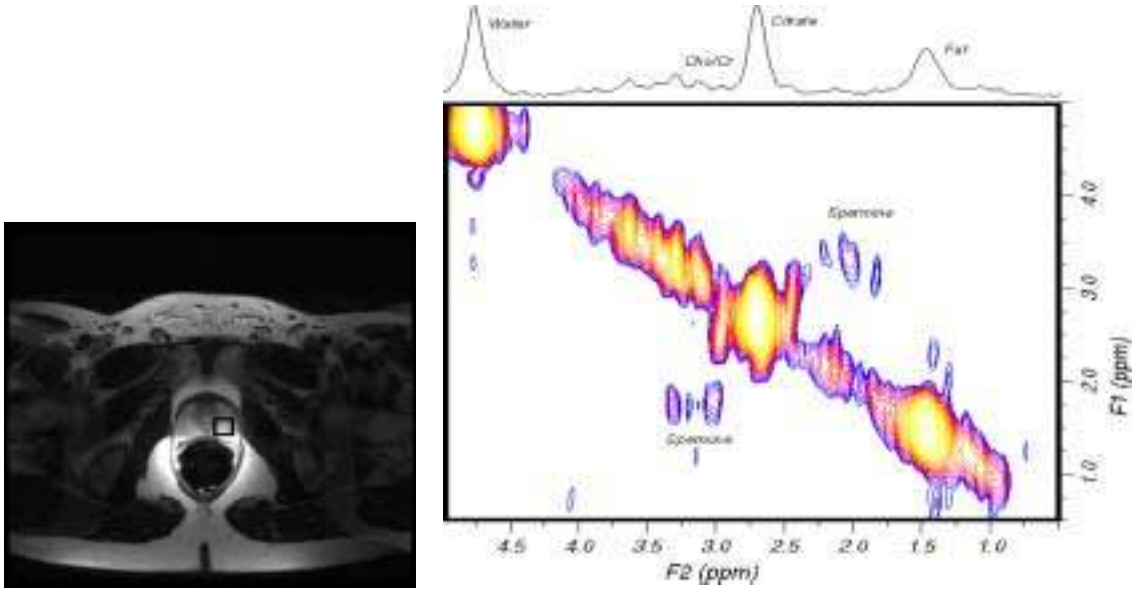


Fig. 2. Simulated 2D L-COSY spectra of citrate, creatine, choline and spermine using a GAMMA library [17]. The 2D spectra were acquired and post-processed using identical parameters used for Fig. 1 except the total number of complex points along the second dimension. The L-COSY sequence for simulation consisted of a binomial (1331) rf pulse followed by hard 180° and 90° rf pulses (TE = 30 ms, 1024 points along F_2 and 128 points along F_1 prior to double Fourier transformation).

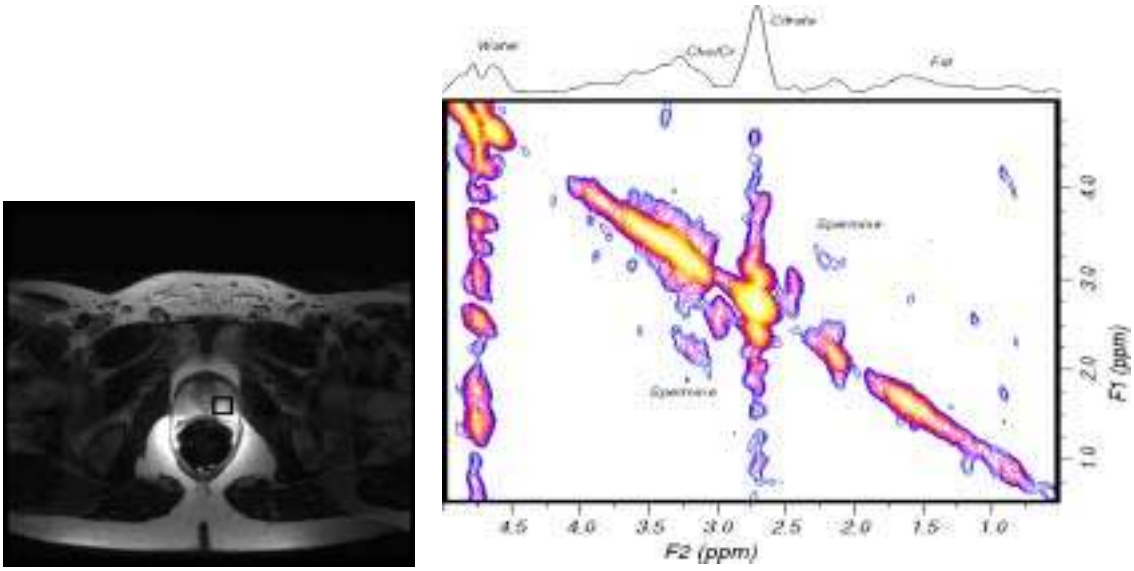


(a) (b)

Fig. 3. (a) The axial MRI of a 28 yo healthy prostate with the voxel used for spectroscopy and (b) the corresponding L-COSY spectrum. A projected 1D MR spectrum is also displayed on top.

future studies using 2D line fitting algorithms could potentially distinguish these individual polyamines. Leibfritz and coworkers have shown that these polyamines can be separated by an indirect detection $^{1}H/^{13}C$ experiments [21].

The 2D cross peaks due to the different choline groups (namely free choline, phosphocholine and ethanolamine) and creatine/phosphocreatine were resolved recently in the human brain [15]. The 2D L-COSY spectra of human prostates did not detect these cross peaks due to the smaller voxel size and lower resolution along F_1 compared to brain 2D scans. We should also mention that L-COSY has an



(a) (b)

Fig. 4. (a) The MRI of a 64 yo BPH prostate with the voxel used for spectroscopy and (b) 2D L-COSY spectrum. A projected 1D spectrum onto the F_2 dimension is also shown.

inferior sensitivity or signal to noise ratio (SNR) when compared with JPRESS (the SNR in COSY is nearly half of that of JPRESS sequence) [15,22]. On the other hand the imperfect 180° rf pulse, which could lead to spurious 2D peaks in JPRESS, are not much of concern in COSY [11].

4. Conclusion

Our preliminary results confirm that endorectal 2D L-COSY spectra can be recorded successfully in human prostates. The total duration for the entire protocol was approximately 45 min. The 2D cross peaks due to spermine/spermidine, citrate, and lipids were recorded. Even though 2D cross peaks due to choline and creatine were recorded in phantoms, they were not recorded *in vivo* when 40–64 increments were used for the second dimension. A high resolution 2D L-COSY spectrum with more than 64 increments may detect these cross peaks. Our pilot findings clearly confirm the potential of localized 2D MRS techniques in separating spermine/spermidine peaks unambiguously from choline and creatine, hence enabling a non-invasive biochemical assay of polyamines and citrate in different prostate pathologies.

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