Measurement of Temperature Distributions in Cryopreservation Solutions using Echo-Planar Spectroscopic Imaging

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Introduction: Development of protocols for cryopreservation of tissues for transplantation requires accurate monitoring of temperature and cryoprotectant concentrations throughout samples during cooling and warming. In this study, spectroscopic magnetic resonance imaging is investigated as a noninvasive method for measuring the spatial and temporal distribution of temperatures in cryoprotectant solutions used for cartilage preservation. Spectroscopic imaging provides a proton spectrum for each image voxel, and differentiates signals originating from water and cryoprotectant. We examine the relationships between temperature, cryoprotectant concentration and the resulting chemical shifts, line widths and *visible* concentrations or water and cryoprotectant protons. We propose that the chemical shift difference ($\Delta\delta$) between water and the cryoprotectant has a simple relationship to temperature allowing for absolute temperature mapping without a reference.

Methods: Cryoprotectant solutions of dimethyl sulfoxide (DMSO) in water at four different concentrations (range 2.5-4.7M) were cooled to -80°C. Samples were warmed inside a 1.5T Siemens Sonata MRI system over 3 hours and imaged at 28 time points to cover a range of temperatures (samples were still visibly frozen in the final experiment). The spectroscopic imaging pulse sequence was based on a conventional gradient echo approach, modified to a train of 1024 echoes, with a 1ms sampling interval for an effective spectroscopic bandwidth of 1000 Hz. Imaging parameters were: 2mm x 2mm in-plane resolution, 128 x 60 matrix, 8mm slice thickness, 2 second repetition time and total acquisition time of 2 minutes. Spectra from individual image voxels (32 µl) from each sample were analyzed. An automated spectral fitting routine was used to quantify the chemical shift, line width and yield of the water and DMSO peaks for all 28 time points and for all four samples.

Results: Spectroscopic analysis at the 28 time points yielded significant variations in several spectral properties including spin density (peak area), line width, and $\Delta\delta$ between water and DMSO peaks. Figure 1 shows sample water and DMSO spectra at the coldest and warmest temperatures from the series of 28 time points (4.7 M DMSO sample). Figure 2 illustrates the dependence of $\Delta\delta$ as a function of temperature and DMSO concentration. A similar trend in water/DMSO solutions has previously been observed[1]. All four concentrations yielded similar results. The DMSO to water signal ratio increased in all four samples as the temperature increased (Figure 3). As shown in Figure 1, there is also a significant reduction in line width with warming, for both water and DMSO peaks.

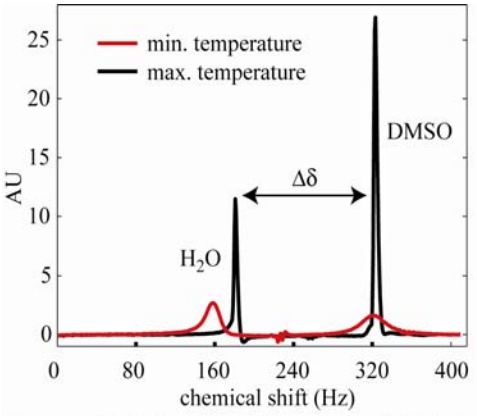

Figure 1 - Variation (linewidths and chemical shifts) in water/DMSO spectra with warming from -80°C.

Conclusion: Spectroscopic imaging of cryoprotectant solutions provides a host of parameters (chemical shifts, line width and visible spin density) in a fast experiment with high spatial resolution. These results confirm the potential for non-invasive temperature mapping and solvent tracking for temperatures as low as -80°C. The presence of DMSO clearly maintains water visibility for sub-zero temperatures (i.e. sufficiently long T_2* to resolve the water and DMSO peaks). This approach offers the potential to measure absolute temperatures using chemical shift differences with high spatial resolution and without need for reference information. This technique could resolve important limitations in current cryobiology research. These studies will be repeated with a newly acquired MRI compatible temperature probe to *quantify* the relationship between the water and DMSO spectral parameters (chemical shifts, line width and visible signal) and temperature. Future studies will transition to cryoprotectant agents in tissue.

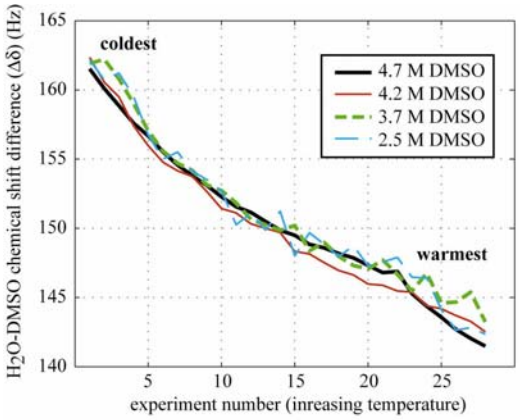

Figure 2 - Chemical shift difference between water and DMSO as a function of temperature and DMSO concentration.

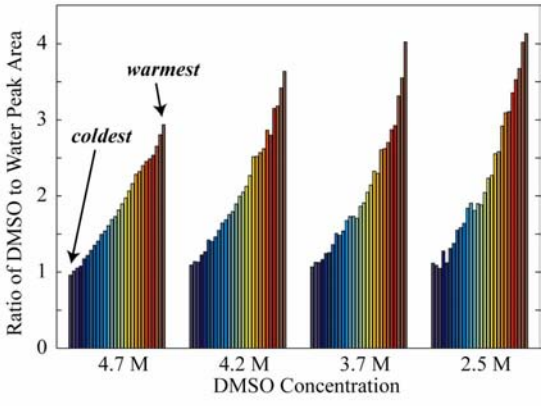

Figure 3 - The ratio of DMSO to water (visible) for the four DSMO concentrations and as a function of temperature.

References: [1] Tokuhiro T, Menafra L and Szmant HH. Contribution of Relaxation and Chemical-Shift Results to Elucidation of Structure of Water-DMSO Liquid-System. *Journal of Chemical Physics* **61**, 2275-2282 (1974).