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Polymer gel dosimetry by Nuclear Overhauser Enhancement (NOE) magnetic resonance imaging

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Abstract

The response to radiation of polymer gel dosimeters has previously been measured by magnetic resonance imaging (MRI) in terms of changes in the water transverse relaxation rate (R_{2w}) magnetization transfer (MT) parameters. Here we report a new MRI approach, based on detecting nuclear Overhauser enhancement (NOE) mediated saturation transfer effects, which can also be used to detect radiation and measure dose distributions in MAGIC-*f*Methacrylic and Ascorbic Acid and Gelatin Initiated by Copper Solution with formaldehyde polymer gels. Results show that the NOE effects produced by low powered radiofrequency (RF) irradiation at specific frequencies offset from water may be quantified by appropriate measurements and over a useful range depend linearly on the radiation dose. The NOE effect likely arises from the polymerization of methacrylic acid monomers which become less mobile, facilitating dipolar through-space cross-relaxation and/or relayed magnetization exchange between polymer and water protons. Our study suggests a potential new MRI method for polymer gel dosimetry.

Keywords

polymer gel dosimetry; nuclear Overhauser enhancement (NOE); magnetization transfer (MT); chemical exchange saturation transfer (CEST); MAGIC gels

1. Introduction

Polymer gel dosimeters comprise various radiation sensitive monomers and other compounds that are distributed in an aqueous matrix. Following irradiation, a variety of chemical reactions may be initiated by free-radical production, and as a result, several physical and chemical properties of the gel may be altered. In particular, polymer particles may be formed in suspension (1–4). Changes in some of these properties vary with the radiation absorbed dose, and measurement of their spatial distributions can therefore be used to map the radiation dose. Previously, different modalities have been used to read out the dose information, including magnetic resonance imaging (MRI) (2,3), optical-computerized tomography (optical-CT) (5), X-ray CT and ultrasound (6). Polymerization is a main consequence of irradiation, which produces radiolysis of water molecules, creates free radicals, and which thereby converts monomers to long-chain polymer particles whose sizes depend on the balance of propagation and termination events within the medium. Polymerization and cross-linking reduce the mobility of protons within the particles and provide a conduit for enhanced relaxation of the bulk water in the gel, thereby increasing the MR transverse relaxation rate (R_{2w}) by through-space dipole-dipole coupling and/or by chemical exchange with labile species (7–9). The loss of mobility by polymerization also facilitates magnetization transfer (MT) effects between the polymer particle protons and water protons (10–13). Conventional MT effects observed in e.g. tissues arise in the presence of very broad and non-specific proton resonances produced by solid-like protons in macromolecules (14) and which are observable above a critical degree of cross-linking in polymers (8). R_{2w} and conventional MT parameters have been the main quantities reported in MRI studies of polymer gel dosimeters to date.

In addition to non-specific MT effects that may be produced by strong irradiation of the broad background line-shape, other types of saturation transfer between water and other protons can be observed. For example, for labile species such as hydroxyls and amides, chemical exchange saturation transfer (CEST) produces decreases in the water signal when their resonant frequencies are saturated and chemical exchange occurs. Such effects are usually observable in small molecules as well as at surfaces of larger structures and depend on the exchange rate and chemical shift of the species, amongst other factors. Another possible interaction between water and solute compounds is a Nuclear Overhauser Enhancement (NOE) which is a type of through-space dipolar interaction between nuclei that are in close proximity to each other (15). Similar to CEST, to observe NOE effects, one nucleus is selectively irradiated, after which the intensity of the signals from dipolar coupled nuclei are also affected. The magnitude and sign of the change depend on the internuclear distance (r_{ij}) and the correlation time of the dipolar field coupling the nuclei. The latter depends on the size and mobility of molecules, or of their internal motions, and the solvent viscosity. NOE effects may also be “relayed” between successive groups or pairs of protons

via spin diffusion within a molecule, so that protons some distance from the original saturation transfer can also show changes in signal intensity. When solvent water is saturated, the loss of magnetization can be transferred via through-space dipolar couplings or via chemical exchange with protons in a solute, after which a relayed NOE effect can be observed on neighboring protons. An essential distinction between relayed NOE effects and conventional MT is that the NOE changes occur over relatively narrow ranges of frequency and arise from more mobile protons than the “semi-solid” nuclei detected by MT, and are detectable using lower powers of RF irradiation (16,17). Here, we describe initial studies of NOE saturation transfer effects in irradiated polymer gels and show how measurable changes in water signal intensities occur with selective irradiations of constituent proton resonances. These measurements scale with absorbed dose and have been used to quantify the radiation dose-response of MAGIC-*f* (Methacrylic and Ascorbic Acid and Gelatin Initiated by Copper Solution with formaldehyde) polymer gels. The results are compared to more conventional measurements of dose by MRI and suggest NOE-based dosimetry may have some advantages over previous approaches.

2. Material and methods

2.1. Sample preparation and irradiation

A conventional MAGIC-*f* gel dosimeter (18) and a modified formulation of the MAGIC-*f* dosimeter were produced for this study. Both are composed of water, gelatin, copper sulfate, methacrylic acid, ascorbic acid, and formaldehyde, in different quantities. Table 1 lists the formulations of the gels. To make the samples, the water was first heated to 50 °C (MAGIC-*f* gel) or 40 °C (modified MAGIC-*f* gel) and the gelatin from porcine skin was added until a homogeneous solution was obtained. The solution was then cooled to 35 °C and the copper sulfate solution, l-ascorbic acid, methacrylic acid, and formaldehyde were added. After manufacture, the mixture was immediately poured into 13 mm diameter plastic tubes sealed with screw-cap tops (to exclude oxygen) and kept in a refrigerator at 4 °C until irradiation. The sample tubes were allowed to warm up to room temperature and put in a cubic acrylic phantom with water to produce appropriate backscattering during the irradiation. To measure the dose-response of the gels, tubes containing MAGIC-*f* gel were irradiated within 24 hours after the sample preparation using a Varian Linear Accelerator in the Department of Radiation Oncology at Vanderbilt University Medical Center, with 6 MV beam and dose rate of 600 MU/min, and doses varying from 0 to 20 Gy. To achieve uniform dose distribution in these tubes, two parallel opposed beams were used. In addition, a uniform cylinder (6 cm diameter) containing modified MAGIC-*f* gel was irradiated with a ¹⁹²Ir high dose brachytherapy source in the Department of Radiation Oncology, University of Arkansas for Medical Sciences, using a Nucletron Microselectron afterloader with a v2 source model. The activity in the day of irradiation was 4.9 Ci, and the prescribed dose was 7.5 Gy to a 0.9 cm from the source center. To deliver the dose into gel, a stainless steel interstitial needle was inserted, and a dwell position was created in the middle of the gel. After the irradiations, the samples were kept in a refrigerator for 24 h until the MRI measurements. All chemicals were purchased from Sigma-Aldrich. For comparisons, samples containing only gelatin (Gel) and only methacrylic acid (MAA) were also prepared but not irradiated.

2.2. MRI

MRI measurements were performed in a 9.4T horizontal magnet using a Varian DirectDrive™ spectrometer and a 38-mm Litz RF coil for imaging the tubes and an 85-mm Doty RF coil imaging the larger phantom (Doty Scientific Inc. Columbia, SC). MR images of the tubes were acquired with a single-shot Echo Planar Imaging (EPI) sequence with matrix size = 64×64, field of view = 30×30 mm², slice thickness = 2 mm, and one acquisition. All images of the larger phantom were acquired with a 2-shot Echo Planar Imaging (EPI) sequence with matrix size = 128×128, field of view = 70×70 mm², slice thickness = 2 mm, and one acquisition. The voxel sizes for the images were 0.47×0.47×2 mm³ for the tubes and 0.55×0.55×2 mm³ for the larger phantom.

The MRI sequence for detecting NOE effects is essentially the same as that for conventional MT or chemical exchange saturation transfer (CEST) imaging in that a long, frequency selective radiofrequency (RF) saturation pulse is implemented, and is then followed by data acquisition. During both MT and CEST imaging, the solute protons are first saturated by the RF pulse, and then they exchange or interact magnetically with water protons. After a few seconds' irradiation, the cumulative effects cause significant decreases in water signal. The concentration of the solute protons can be estimated by measuring the change in water signal. The higher the RF power and/or the longer the RF pulse, the greater the saturation of the solute protons. Fig. 1 shows the sequence diagram. A Z-spectrum is a plot of the measured water signal as a function of the RF irradiation frequency, and is obtained by varying the saturating pulse frequency offset from water. Specific dips (peaks) in a Z-spectrum occur at the offsets corresponding to chemical shifts of different protons that interact with the water. Non-exchanging aliphatic resonances often appear upfield of water, while several species such as hydroxyls and amides are downfield. Conventional MT effects do not usually show resolvable peaks and can be obtained far from, and on either side, of the water resonance. The relative magnitudes of NOE, MT and CEST effects depend on the RF power used as well. In this study, a continuous wave (CW) RF pulse with irradiation powers (B_1) of 0.5 μ T, 1 μ T, and 1.5 μ T, pulse duration of 5 s, and delay time (time between the end of one RF pulse and the beginning of the next, see Fig. 1) of 2 s was used to irradiate solute protons. Z-spectra were acquired with RF frequency offsets from -2000 Hz to 2000 Hz (-5 ppm to 5 ppm at 9.4 T) with an interval of 50 Hz (0.125 ppm at 9.4 T). A control scan was performed to acquire a reference signal (S_0) by setting the RF frequency offset to 100,000 Hz (250 ppm at 9.4 T). In addition, the water transverse relaxation rate R_{2w} was obtained by using a spin-echo sequence with echo times (TE) of 30, 180, 250, and 400 ms and time of repetition (TR) of 4 s. The echo data were fit to a monoexponential decay curve pixel by pixel-wise to obtain R_{2w} maps for different doses. A high resolution ¹H NMR spectrum of the MAA sample was obtained using a point-resolved spectroscopy (PRESS) sequence with VAPOR water suppression (19) and the following parameters: spectral width = 4 kHz, number of points = 4096, number of acquisitions averaged = 512, TE1 = 8 ms, TE2 = 7 ms, and TR = 3 s.

2.3. NOE quantification method

The magnitude of the NOE effects on water depend on multiple parameters including the water longitudinal relaxation time (T_{1w}), the magnitude of direct saturation of the water by

the saturating RF (DS), which depends on both T_{1w} and T_{2w} , and the bandwidth and power of the RF pulses, and conventional MT effects (20). An analysis of the asymmetry of Z-spectra is typically used to reduce the influence of DS and conventional MT effects by assuming that there are negligible saturation transfer effects at the symmetric frequency offsets to each detectable peak (21). The quantity MTR_{asym} is defined to be the difference of the measured signals from water protons when a specific peak is irradiated (S_+ , the label signal) compared to irradiating at equal offset on the opposite side of the water line (S_- , comparison signal) (21), normalized to the reference signal S_0

$$MTR_{\text{asym}} = \frac{S_+ - S_-}{S_0} \quad (1)$$

However, recent studies have shown that NOE, CEST, DS, and conventional MT effects can have mutual interactions, and do not add linearly (22). Thus MTR_{asym} cannot fully remove DS and conventional MT effects (22–24) and they may detract from the accuracy of measuring true NOE or CEST effects when DS and MT are significant. To further reduce the influence of these factors, a modified analysis subtracts the reciprocals of the label and comparison signals and calculates a different metric, MTR_{Rex} (22–24).

$$MTR_{\text{Rex}} = \left(\frac{S_0}{S_-} - \frac{S_0}{S_+} \right) \quad (2)$$

Here, we used MTR_{Rex} to quantify NOE effects in irradiated gels. Our measurements on the MAGIC-*f* samples with different doses show no significant changes in T_{1w} (data not shown), we do not correct for T_{1w} variations.

2.4. Sensitivity and Dose resolution

There is no single metric that describes the performance of gels as dosimeters. One approach is the dose resolution with 95% level of confidence ($D^{95\%}$) (6,25) which was calculated as,

$$D_{\Delta}^{95\%} = 2.77\sigma_D \quad (3)$$

$$\sigma_D = \sigma_P/k \quad (4)$$

where σ_D and σ_P are the standard deviation of dose and MR parameters, respectively; k is the fitted slope of the calibration curve of MR parameters versus dose.

3. Results

Fig. 2a shows the variation of $R2w$ with irradiation dose for MAGIC-*f* samples along with the least squares linear regression fit over the range 0 to 20 Gy. As expected, the dose-

response is well-described by a linear fit up to 20 Gy with slope $0.69 \text{ sec}^{-1}\text{Gy}^{-1}$ ($r = 0.99$, $p = 7.0 \times 10^{-5}$). The slope is approximately half of previous reports performed at lower fields (e.g. (26)). Fig. 2b shows $D^{95\%}$ for the R_{2w} measurement over the same range.

Fig 3 shows the measured high resolution ^1H NMR spectrum of MAA which is consistent with publicly available data (https://www.chemicalbook.com/SpectrumEN_79-41-4_1HNMR.htm), along with its chemical structure. There are prominent peaks at -3 ppm, $+0.8$ ppm, and $+1.2$ ppm from water which originate from the CH_3 group and two CH protons respectively. The COOH proton in MAA resonates at $+11.3$ ppm, beyond our spectral window.

Fig. 4 shows Z-spectra obtained for MAGIC- f samples irradiated to different doses acquired with different B_1 . At lower RF pulse powers, as radiation dose increases, large, well resolved dips arise at -3 ppm as well as at 0.8 ppm, 1.2 ppm, with smaller effects elsewhere. At higher powers the background spectrum shows increasing effects from non-specific MT and the peaks are less well resolved. However, the negative dips clearly increase in magnitude at high doses. These dips, corresponding to the frequencies of the non-exchanging protons in MAA, are NOE effects from saturation transfer from the water.

Figs. 5 and 6 show MTR_{asym} and MTR_{Rex} spectra, respectively, of MAGIC- f samples irradiated to different doses acquired with different B_1 . The negative values close to the water line arise from NOEs at $+0.8$ ppm and $+1.2$ ppm because the plot shows only one side of the water resonance.

Fig. 7 plots the values of MTR_{asym} and MTR_{Rex} for the -3 ppm NOE only against radiation dose for different B_1 . At low RF power ($B_1 = 0.5 \mu\text{T}$) both MTR_{asym} and MTR_{Rex} show a linear dependence ($r = 1$ and 0.99 , $p = 1.3 \times 10^{-5}$ and 1.1×10^{-4} , respectively) on radiation dose. At higher RF powers, MTR_{asym} becomes less linear with dose as the increased DS and conventional MT effects at higher B_1 values influence its value. In contrast, MTR_{Rex} acquired with all B_1 powers show roughly linear dependences on the radiation dose ($r = 0.99$ and 1 , $p = 5.6 \times 10^{-5}$ and 1.1×10^{-5} for B_1 of $1 \mu\text{T}$ and $1.5 \mu\text{T}$, respectively). Fig. 8 shows $D^{95\%}$ for the NOE measurements. Note that the NOE measurements have roughly similar dose resolution as those of R_{2w} measurements in Figure 2 with our sequence parameters.

Fig. 9 shows maps of MTR_{Rex} at -3 ppm and R_{2w} for the modified MAGIC- f sample irradiated with a brachytherapy source. The higher values around the center of the sample indicate higher radiation dose. Fig. 10a and 10b plots the values of MTR_{Rex} at -3 ppm and R_{2w} as a function of the distance from the sample center. Note that both curves show an exponential decay. However, although MTR_{Rex} at -3 ppm decreases to roughly 0 with distance from the sample center, R_{2w} approaches the background value of the unirradiated gel. To compare the two methods, we removed the background value on the R_{2w} curve and scaled it to obtain a normalized R_{2w} curve so that it could be plotted together with the curve of MTR_{Rex} at -3 ppm in the same figure. Fig. 10c compares the two curves. Note that the two curves match well, suggesting that the NOE is an alternative method to R_{2w} to measure dose distribution.

4. Discussion

In this study, we show that NOE effects acquired with low RF irradiation powers and quantified using MTR_{Rex} can be used to measure radiation absorbed doses in polymer gels. The dose resolution of the NOE from the methyl group in methacrylic acid is roughly similar to R_{2w} with our sequence parameters and is linear up to 20 Gy at the field used here. Fig. 4 shows that there are no measurable NOE effects at -3 ppm from samples without radiation, but there are residual influences from downfield saturation transfer effects that cannot be removed by the asymmetric analysis. These downfield saturation transfer effects cause a bias in the dose estimates, resulting, for example, in negative intercepts in the dose response curves of Fig. 7. However, the negative intercepts are relatively very small at low RF irradiation powers (e.g. $0.5 \mu\text{T}$ and $1 \mu\text{T}$) when the downfield saturation transfer effects are narrow and weak. Asymmetry of conventional MT effects has been found in biological tissues (27), which can also cause a bias in the quantification of CEST or NOE. Asymmetric MT effects have not been reported for MAGIC-*f*gels but the asymmetric analysis in Fig. 5 indicates that it must be very small compared with the NOE effect. To be more accurate, several other quantification methods (e.g. multiple-Lorentzian line fitting (20,28), or chemical exchange rotation transfer (CERT) (29,30)), which have even smaller effects from the downfield saturation transfer and/or the conventional MT asymmetry could be adapted to quantify the NOEs and achieve higher sensitivity.

Radiation is known to cause the MAA to polymerize and form large molecules. The overlap of the observed NOE effects with the chemical shifts of the methyl and methylene protons in MAA implies these are the protons that are affected by the saturation transfer. Moreover, there are no measurable NOE effects in MAA (or in MAGIC-*f*gels) before radiation, consistent with a model in which polymerization produces particles in which more rigid chains are formed so that proton mobility is decreased, increasing the correlation times of the proton dipolar interactions and allowing a negative NOE to arise. One possible conduit for the saturation transfer is via direct through-space dipolar coupling of the slowly-tumbling methyl and methylene protons with water protons at the surface of the polymerized particles. A second possibility is that after selective saturation of the methyl or methylene protons, spin diffusion through the polymer relays the saturation to the COOH proton which in turn affects the water by chemical exchange. The latter mechanism would be expected to be strongly pH dependent and further studies to establish the precise pathway for saturation to affect the water are required.

This is a first proof-of-principle study of NOE effects in a polymer gel. These and other results provide useful insights into the dose response mechanism of this and related gels. They also may lead to new directions for developing improved gel formulations. For example, gelatin is used as the background matrix in MAGIC-*f*gels and is suitable because it provides a low background value of R_{2w} . However, different considerations may apply to the design and performance of NOE-based gels in which it is desirable to minimize saturation transfer effects other than at relevant parts of a Z-spectrum. Although we studied the NOE effects in MAGIC-*f*gels in this paper, other gels which contain polymerized acrylic monomers should also show NOE responses. Our measurements were performed on a 9.4 T MR system. At lower fields, the DS and MT effects may be stronger, and the peaks in a Z-

spectrum are less well separated. Lower RF powers may be used to reduce these problems. Future studies may evaluate the feasibility of using NOE detection on clinical scanners and compare it with R_{2w} with optimized sequence parameters. Future studies should also compare the NOE distribution in gels with other reading techniques (e.g. gafchromic film).

5. Conclusion

We perform a proof-of-the-principle study to show that MR NOE effects can be used to detect radiation deposition in a polymer gel.

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Fig. 1:
MRI sequence diagram for detecting NOE effect.

Fig. 2:
 R_{2w} (a) and the corresponding $D_{\Delta}^{95\%}$ (b) on MAGIC- f samples with different radiation doses. Error bars in (a) are the standard deviations across pixels on R_{2w} maps.

Fig. 3:
 ^1H MRS spectrum (a) and the chemical structure (b) of MAA sample.

Fig. 4:
Z-spectra on MAGIC-f samples with different radiation doses showing NOE and other saturation transfer effects (arrow) with B_1 of 0.5 μ T (a), 1 μ T (b), 1.5 μ T (c).

Fig. 5:
MTR_{asymp} spectra on MAGIC-*f* samples with different radiation doses showing NOE effects with B₁ of 0.5 μT (a), 1 μT (b), 1.5 μT (c).

Fig. 6: MTR_{Rex} spectra on MAGIC-*f* samples with different radiation doses showing NOE effects with B_1 of 0.5 μT (a), 1 μT (b), 1.5 μT (c).

Fig. 7:

MTR_{asy} and MTR_{Rex} values at -3 ppm on MAGIC-*f* samples with different radiation doses showing NOE effects with B₁ of 0.5 μT (a, d), 1 μT (b, e), 1.5 μT (c, f). Error bars are the standard deviations across pixels on the corresponding maps.

Fig. 8:

$D_{\Delta}^{95\%}$ on MAGIC- f samples with different radiation doses for MTR_{asy} at -3 ppm with B_1 of 0.5 μ T (a), MTR_{Rex} at -3 ppm with B_1 of 0.5 μ T (b), 1 μ T (c), and 1.5 μ T (d). Note that only $D_{\Delta}^{95\%}$ on the sample with 0 Gy radiation in (c) (7.2) is beyond the figure.

Fig 9:
Maps of MTR_{Rex} at -3 ppm (a) and R_{2w} (b) on a modified MAGIC-*f* sample irradiated in the brachytherapy source. NOE data were obtained with B_1 of 1 μT .

Fig 10.

Signals of MTR_{Rex} at -3 ppm (a) and R_{2w} (b) vs. distance from the center of the sample on a modified MAGIC-*f* sample irradiated in a brachytherapy source. NOE data were obtained with B_1 of 1 μT . Signals were obtained from voxels on a line (with width of 4.9 mm and 9 pixels) from the center to the right edge of the sample. Error bars are the standard deviations across the 9 pixels. (c) compares the mean value of the MTR_{Rex} at -3 ppm and a normalized R_{2w} vs. distance from the center of the sample. The normalized R_{2w} curve was obtained by first removing the background value by subtracting the R_{2w} curve with the R_{2w} value at the far right point, and then scaling to match a point at 4.4 mm from the center on the curve of MTR_{Rex} at -3 ppm.

Table 1.

The mass concentration (%) of the MAGIC-*f* and modified MAGIC-*f* gel.

MAGIC- <i>f</i>	Modified MAGIC- <i>f</i>
82.31 Deionized Water	78.91 Deionized Water
8.33 Gelatin	11.00 Gelatin
0.02 Copper Sulfate Pentahydrate	0.02 Copper Sulfate
0.03 Ascorbic Acid	0.08 Ascorbic Acid
5.99 Methacrylic Acid	5.99 Methacrylic Acid
3.32 Formaldehyde	4.00 Formaldehyde