A PHANTOM MATERIAL FOR MRI OF THE NEONATAL BRAIN

Timothy N. Orr[1,2], Jeff Winter[1,2], Gordon Campbell[2,3], R. Terry Thompson[1,2], Neil Gelman[1,2]

[1]Imaging Division, Lawson Health Research Institute, London, ON, Canada, [2]Department of Medical Biophysics, University of Western Ontario, London, ON, Canada, [3]Integrated Manufacturing Technologies Institute, National Research Council, London, ON Canada

INTRODUCTION

Studies [1-3] have shown that magnetic resonance imaging (MRI) techniques can be used to non-invasively investigate the impact of premature birth on early brain development, and to provide prognostic indicators of neuro-developmental outcome. Optimization (at a given field strength) and adaptation of relevant MRI sequences developed for adults need substantial revision because the relaxation times (T_1 and T_2) of neonatal brain tissues [4] differ greatly from those of adults and children. Image constrast and information is largely determined by T_1 and T_2. Experimental testing of these MRI techniques would be useful, not only for optimizing contrast, but also for exploring the influence of imaging parameters on the efficacy of image processing techniques such as segmentation. However, performing optimization of MRI sequences on human neonates is not ethically appropriate. Also, animal models with appropriate relaxation times and morphology are not easily available. Digital phantoms would also not be optimal because of the difficulties associated with accounting for "non-ideal" signal behaviour from various sources (e.g. imperfect spoiling, eddy currents, non-uniform static and radio-frequency magnetic fields). Thus, a realistic phantom to mimic both the MR parameters (T_1 and T_2) and morphological features of the neonatal brain would be a valuable tool.

In order to develop a brain phantom for neonatal MRI, it is necessary to choose a phantom material that can be molded into a complex shape. Polyvinyl alcohol cryogel (PVA-C), a non-toxic gel that is prepared by applying one or more freeze-thaw cycles (FTCs) [5], has been utilized for various structural biomedical applications [6], demonstrating its potential for complex molding. PVA-C has also been explored as a MRI phantom material [7], and has been used to create a single compartment homogenous adult brain phantom [8]; thus demonstrating that its shape-retaining properties are adequate for brain phantom construction.

The first stage in the creation of a neonatal brain phantom involves the development of appropriate tissue-mimicking materials for neonatal white matter (WM) and grey matter (GM). One challenge associated with this is emulating the very long relaxation times of neonatal WM, in which T_1 exceeds 2800 ms at 3.0 T [4]. The difficulty in achieving T_1 relaxation times sufficiently long to represent neonatal WM is not unexpected since T_1 of water increases substantially with temperature, and the temperature of human brain tissues (37°C) is greater than the phantom temperature (≈20-25°C) used for most applications. Our approach in achieving the required long relaxation times of neonatal brain tissues involves imaging the phantom material at a higher temperature.

A second challenge involved in creating a neonatal brain phantom is independently altering both T_1 and T_2 of the phantom material. Previous studies [5,9] have shown that this can be accomplished using two or more additives. Certain additives have the ability to influence T_2 more strongly than T_1. We have chosen to use agarose for this purpose.

The objective of the present study was to investigate the possibility of emulating neonatal white matter (WM) and grey matter (GM) with a phantom material based on PVA-C, containing agarose as an additive. In this work, we explore the influence of temperature and PVA-C concentration (1 FTC) on relaxation times, in order to determine if sufficiently long T_1 values to represent neonatal WM can be achieved by altering these two parameters. Then we investigate the influence of agarose concentration for various PVA-C concentrations on the relaxation times measured at an elevated target temperature (40°C). Using the results obtained from this study, we will determine the concentrations of PVA-C and agarose required to emulate the relaxation times of neonatal WM and GM with samples held at 40°C.

METHODS

Sample Preparation

Samples of PVA-C for each concentration (3, 6, 10, 15%; [PVA]/[H_2O]; w/w) were prepared with 1 cycle of freezing/thawing using a standardized method [10]. A second set of samples (3, 6, 11, 15%; [PVA]/[H_2O]; w/w) containing agarose (0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.4, 1.8%; w/w) as an additive was also prepared. The samples were stored in water and refrigerated at 4°C for approximately 4 weeks before imaging.

Sample Warming

The samples were heated in a water bath and held at a fixed temperature for 30 minutes. After heating, the samples were placed in an insulated styrofoam container and then placed in the RF coil for MRI scans. Measurements were performed at 5 different temperatures (20, 25, 30, 35, 40°C) for the first set of samples and one temperature (40°C) for the second set.

Imaging

MRI was carried out on a custom built 3.0 T MRI system. Image-based measurements of T_1 were obtained using the TOMROP pulse sequence [11], implemented as previously described [12]. Image-based measurements of T_2 were obtained using a 16-segment spin-echo echo-planar imaging sequence as previously described [4].

Regression Analysis

The measured relaxation times for the first set of samples were fit to the following model:

$$T_i = a_0 + a_1[P] + a_2T + a_3[P]T \quad (1)$$

where T_i=T_1 or T_2, [P]=PVA%, T=temperature.

Relaxation times for the second set of samples (all at 40°C) were fit to the following models:

$$T_1 = c_0 + c_1[P] + c_2[A] + c_3[P][A] \quad (2)$$

$$T_2 = (b_0 + b_1[P]) + (b_2 + b_3[P])\exp\{-[A](b_4 + b_5[P])\} \quad (3)$$

where [A]=agarose%. Optimal Values of all adjustable parameters (a0 to a3, b0 to b5, c0 to c3) were determined using the Gauss-Newton method.

RESULTS

Figures 1 and 2 illustrate the measured relaxation times of PVA-C as a function of temperature, as well as the regression model (Eq. (1)). Error bars represent standard deviations. The model function (Eq. (1)) provides a good match to the data within this range of temperatures and PVA-C concentrations, with these two variables accounting for almost all the observed variance (R^2 = 0.99 and R^2 = 0.98 for T_1 and T_2, respectively). Horizontal lines on these figures represent mean T_1 and T_2 values previously obtained for neonatal WM and GM at 3.0 T [4].

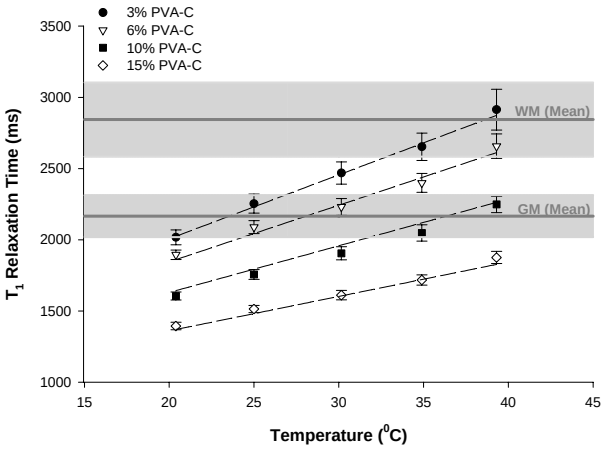

Figure 1: T_1 of PVA-C vs. Temperature. Mean T_1 values [4] for neonatal WM (upper line) and GM (lower line) with standard deviations (shaded) are shown.

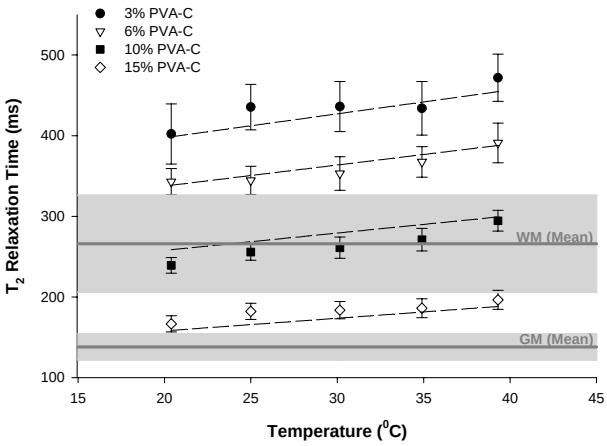

Figure 2: T_2 of PVA-C vs. temperature. Mean T_2 values [4] for neonatal WM (upper line) and GM (lower line) with standard deviations (shaded) are shown.

From Fig. 1, it is evident that T_1 values sufficiently long to represent neonatal WM (mean T_1 = 2844 ms) are obtained with [P] ≈ 3% and T ≈ 40°C. At this temperature, the T_1 of GM (mean T_1 = 2166 ms) is obtained with [P] ≈ 11%. The corresponding T_2 values (≈ 440 ms and ≈ 270 ms for 3% and 11% PVA-C, respectively) at 40°C (Fig. 2) are too long for neonatal WM (mean T_2 = 266 ms) and GM (mean T_2 = 138 ms).

Measured T_2 and T_1 values for the PVA-C samples with agarose at 40°C are illustrated in Figures 3 and 4, along with the regression models (Eq. (2) & (3)). The model functions (Eq. (2) & Eq. (3)) provide good matches to the data within this range of agarose and PVA concentrations, with these two variables accounting for almost all of the observed variance (R^2 = 0.98 and R^2 = 0.99 for T_1 and T_2 respectively).

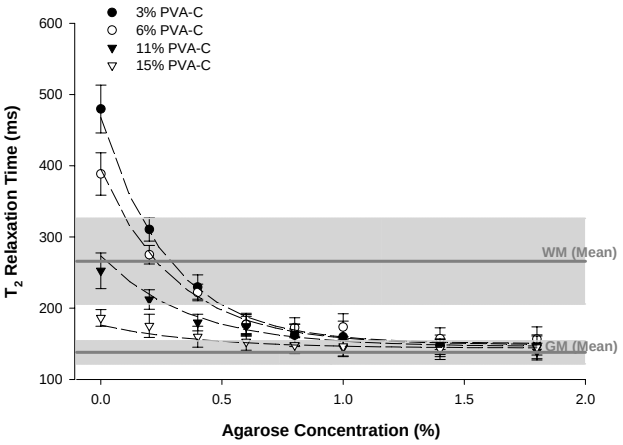

Figure 3: T_2 of PVA-C vs. agarose concentration at 40°C. Mean T_2 [4] for neonatal WM (upper line) and GM (bottom line) with standard deviations (shaded) are shown.

These figures illustrate that by adding agarose to PVA-C as measured at 40°C, it is possible to substantially shorten T_2 (Fig. 3) while only moderately affecting T_1 (Fig. 4). With the addition of agarose, T_2 values (Fig. 3) level off close to the mean T_2 value reported [4] for neonatal GM at 3.0 T (bottom horizontal line). Using both regression models, it was determined that T_1 and T_2 of neonatal WM can be mimicked using [P] ≈ 3% and [A] ≈ 0.3%, and that T_1 and T_2 for neonatal GM can be approximately achieved (with T_2 slightly above the mean value (Fig. 3)) using [P] ≈ 8% and [A] ≈1.4%.

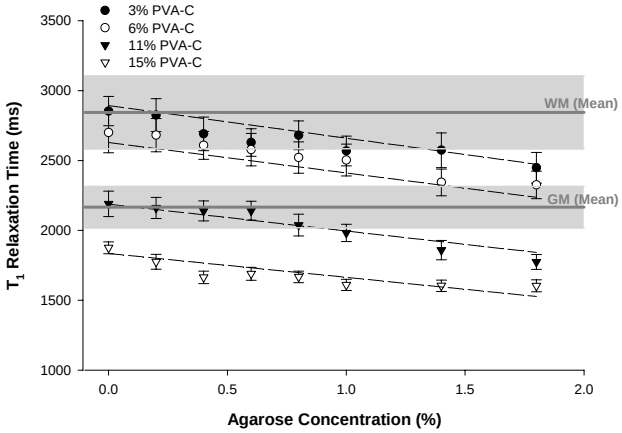

Figure 4: T_1 of PVA-C vs. agarose concentration at 40°C. Mean T_1 [4] for neonatal WM (upper line) and GM (bottom line) with standard deviations (shaded) are shown.

DISCUSSION

In this work we investigated the feasibility of creating composite phantom materials to emulate the MRI relaxation times of the neonatal brain at 3.0 T using polyvinyl alcohol cryogel (PVA-C) as a base material and agarose as an additive. Our results demonstrate that it is possible to emulate the long T_1 values of neonatal WM by raising the temperature of low concentration PVA-C to approximately 40°C. By combining this approach with the addition of agarose, both T_1 and T_2 values of the tissues can be approximately emulated. To our knowledge this is the first work to explore temperature dependence of the relaxation times of PVA-C, to explore MRI properties of very low concentration PVA-C (< 10% by wt) and to study relaxation times of this material at 3.0 T.

For the present work, we chose to increase sample temperature in order to achieve the required long T_1 values of neonatal WM. Two other potential methods for lengthening T_1 should be considered. The first involves “preheating of samples” [13], a technique previously developed for temperature dosimetry. In this previous study [13], PVA-C samples (10% & 15% PVA-C with 1 FTC and 10% PVA-C with 2 FTCs) were heated to temperatures up to 72°C, and then cooled to 20°C prior to MRI measurements. This led to lengthening of T_1 and T_2 as measured within 10 hours after preheating; however, the relaxation times for the 10% sample with 1 FTC (most relevant to our work) were not stable as assessed two weeks later. In addition, one would expect that heating of PVA-C to such high temperatures could alter its polymer structure and possibly its mechanical properties. Another possible

method of lengthening T_1 involves reducing dissolved oxygen levels in samples. In a previous study [14], it was reported that removal of dissolved oxygen from bovine serum albumin samples caused only a 5% increase in T_1. Thus, removal of sample oxygen would not likely provide a sufficient T_1 increase.

Our results indicate that we can achieve T_1 and T_2 values corresponding to the mean reported 3.0 T values for neonatal WM. However, for emulating neonatal GM our closest approximation would have T_2 values (150 ms) that are slightly above the mean reported value (mean T_2 = 138 ms, SD = 16 ms). This would still provide a reasonable emulation of neonatal GM. It might be possible to achieve a shorter T_2 value while maintaining the required T_1 by increasing the number of FTCs that the PVA-C undergoes.

The information obtained in this present study represents the first step in the design and construction of a multi-region MRI brain phantom with morphology and relaxation times appropriate for neonatal brain tissue. In order to utilize such a phantom for testing and optimizing MRI techniques (e.g. 3D imaging), it would be necessary to hold the phantom temperature at 40°C for at least a period of roughly one hour or more. In the present study, with the phantom materials held in a styrofoam container (2.9 cm wall thickness), the temperature of the samples that were initially close to 40°C dropped by less than 1.5°C over the 45 minute imaging duration. However, heat loss could be reduced by increasing the wall thickness of the styrofoam. Assuming a neonatal brain phantom with a 10 cm diameter, imaged in the same RF coil used in this study (27.9 cm inside diameter), one could construct a cylindrical insulator with wall thickness of approximately 9 cm (approximately 3 times thicker than that used here). If necessary, a vacuum-based insulated container could also be used.

In summary, we have shown that the relaxation times of neonatal brain tissues can be emulated at 3.0 T using polyvinyl alcohol cryogel (PVA-C) as a base phantom material and agarose as an additive. This can be achieved by increasing the temperature of the phantom material to 40°C. At this temperature, neonatal WM can be mimicked with a PVA-C concentration of 3% and an agarose concentration of 0.3%. Neonatal GM can be closely mimicked (with T_2 values slightly above the mean reported value) with a PVA-C concentration of 8% and an agarose concentration of 1.4%.

ACKNOWLEDGEMENTS

Financial support from the Canadian Institute for Health Research (CIHR), Canadian Foundation for Innovation (CFI), the Ontario Research and Development Challenge Fund (ORDCF) and Multi-Magnetics Inc. (MMI) are gratefully acknowledged.

REFERENCES

[1] Vasileiadis G, Gelman N, Han V, Williams L, Mann R, Bureau Y, and Thompson RT (2004). "Uncomplicated intraventricular hemorrhage is followed by reduced cortical volume at near-term age", *Pediatrics*, vol. 114, pp. e367-e372.

[2] Inder T, Wells S, Mogridge N, Spencer C, Volpe J (2003). "Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study", *J. Pediatr.*, vol. 143, pp. 171-179.

[3] Murphy B, Inder T, Huppi P, Warfield S, Zientara G, Kikinis R, et al. (2001). "Impaired Cerebral Cortical Gray Matter Growth After Treatment With Dexamethasone for Neonatal Chronic Lung Disease", *Pediatrics*, vol. 107: pp. 217-221.

[4] Williams L, Gelman N, Picot P, Lee D, Ewing J, Han V, Thompson RT (2005). "Neonatal brain: regional variability of in vivo MR imaging relaxation rates at 3.0 T – initial experience", *Radiology*, vol. 235: pp.595-603.

[5] Mano I, Goshima H, Nambu M, Iio M (1986). "New polyvinyl alcohol gel material for MRI phantoms", *Magn Reson. Med.*, vol. 3: pp. 921-926.

[6] Jiang H, Campbell G, Boughner D, Wan W, and Quantz M (2004). "Design and manufacture of a polyvinyl alcohol (PVA) cryogel tri-leaflet heart valve prosthesis", *Med. Eng Phys.*, vol. 26: pp. 269-277.

[7] Chu K and Rutt B (1997). "Polyvinyl alcohol cryogel: an ideal phantom material for MR studies of arterial flow and elasticity", *Magn Reson. Med.*, vol. 37: pp. 314-319.

[8] Surry K, Austin H, Fenster A, and Peters T (2004). "Poly(vinyl alcohol) cryogel phantoms for use in ultrasound and MR imaging", *Phys. Med. Biol.*, vol. 49: pp. 5529-5546.

[9] Yoshimura K, Kato H, Kuroda M, Yoshida A, Hanamoto K, Tanaka A, et al. (2003). "Development of a tissue-equivalent MRI phantom using carrageenan gel", *Magn Reson. Med.*, vol. 50: pp. 1011-1017.

[10] Paliy I, Gelman N, Campbell G, Winter J, and Thompson RT (2004). "MRI Properties of Polyvinyl Alcohol Cryogel, Potential Material for Neonatal Brain Phantoms", submitted for Thirteenth Annual Meeting of ISMRM.

[11] Brix G, Schad L, Deimling M, and Lorenz W (1990). "Fast and precise T1 imaging using a TOMROP sequence", *Magn Reson. Med.*, vol. 8: pp. 351-356.

[12] Gelman N, Ewing J, Gorell J, Spickler E, and Solomon E (2001). "Interregional variation of longitudinal relaxation rates in human brain at 3.0 T: relation to estimated iron and water contents", *Magn Reson. Med.*, vol. 45: pp. 71-79.

[13] Lukas L, Surry K, and Peters T (2001). "Temperature dosimetry using MR relaxation characteristics of poly(vinyl alcohol) cryogel (PVA-C)", *Magn Reson. Med.*, vol. 46: pp. 1006-1013.

[14] Kettunen M, Grohn O, Silvennoinen M, Penttonen M, Kauppinen R (2002). "Effects of intracellular pH, blood and tissue oxygen tension on T1rho relaxation in rat brain", *Magn Reson. Med.*, vol. 48: pp. 470-477.