

NMR in Experimental Cerebral Edema: Value of T1 and T2 Calculations

M. Brant-Zawadzki¹
 H. M. Bartkowski²
 D. A. Ortendahl^{1,3}
 L. H. Pitts²
 N. M. Hylton³
 M. C. Nishimura²
 L. E. Crooks³

In an experimental investigation, the efficacy of nuclear magnetic resonance (NMR) relaxation times in measuring brain water was studied. Cerebral edema was induced in four dogs with a freeze lesion, which was produced by contact with a steel cylinder cooled in liquid nitrogen and placed on the exposed dural surface of the brain. NMR proton imaging was performed 2, 3, 6, or 24 hr after production of the lesion, at a field strength of 0.35 T, using multiparametric spin-echo (SE) technique. The animals were sacrificed immediately after imaging, and brain samples were analyzed for water content (wet-to-dry, microgravimetry). Correlation between water content, NMR imaging, and resulting T1, T2 relaxation times and mobile proton density values calculated with SE technique was performed.

Brain sample analysis showed elevation of water content in the white matter subjacent to the lesion in all four dogs, rising at least 15% in each of the animals. NMR imaging detected the freeze lesion and subjacent vasogenic edema of the white matter in all animals. The 2 sec pulse interval SE technique was most sensitive in the detection of the abnormality, and provided optimal differentiation of gray and white matter. The second echo sampling (56 msec) was most sensitive to the detection of edema. The T1 and T2 relaxation values, as well as the mobile proton density values, were elevated in the normal gray matter and in the abnormal white matter when compared with normal white matter in any given animal. Although absolute T1 and T2 relaxation values proved of little use in comparing different animals, the difference between normal and abnormal white matter in a given animal was comparable to such differences in the other animals. The differences between normal gray and white matter T1 or T2 relaxation value also were comparable in the four animals, whereas absolute T1 or T2 values for the gray or the white matter showed little correlation from animal to animal.

A crucial requirement of any diagnostic modality, including nuclear magnetic resonance (NMR), for evaluation of the central nervous system is sensitivity to changes in the water content of tissues. This is necessary because a wide range of pathology produces edema in brain and spinal cord. Indeed, NMR appears to fulfill this requirement and has proven to be quite useful in evaluating diseases of the neural axis, showing not only alteration of normal anatomy but also depicting changes in tissue characteristics [1-7].

However, multiple imaging sequences are available with NMR, and optimal sequences for defining anatomy are not necessarily the most sensitive for detecting pathology. Our experience with the spin-echo (SE) technique suggests it can fulfill both needs. The purpose of this study was to define that sequence within the SE technique that best detects and depicts brain edema, and to analyze the usefulness of calculated T1 and T2 relaxation data on the basis of this technique in quantifying such edema.

Materials and Methods

Four mongrel dogs (25-35 kg) had burr holes placed with a twist drill over the right cerebral

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¹ Department of Radiology, University of California C-309, San Francisco, CA 94143. Address reprint requests to M. Brant-Zawadzki.

² Department of Neurosurgery, University of California, San Francisco, CA 94143.

³ Radiologic Imaging Laboratory, University of California, South San Francisco, CA 94080.

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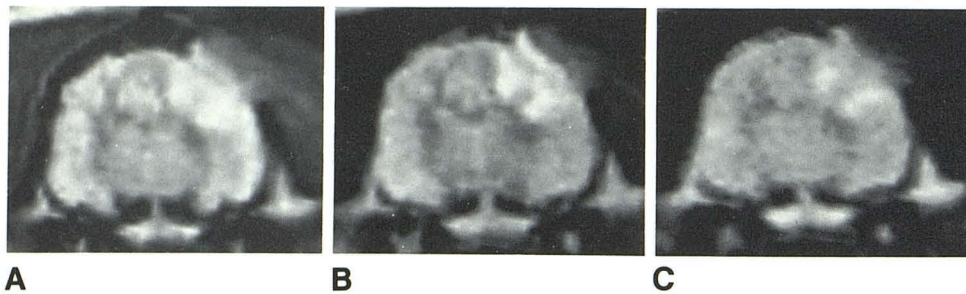


Fig. 1.—Freeze lesion. SE technique, coronal section. A, TR = 2000 msec, TE = 28 msec. Gray and white matter are easily separable, ventricles delineated, and lesion in right hemisphere is seen. B, TR = 2000 msec, TE = 56 msec. Second echo provides image with greater contrast between edematous and normal brain than first echo (cf. A). C, TR = 1000 msec, TE = 56 msec. Despite suboptimal delineation of anatomy and gray-white matter difference, lesion can be discerned on image obtained with second echo.

convexity after routine anesthesia. A steel cylinder 2.4 cm in diameter was cooled in liquid nitrogen and then placed on the exposed dural surface of each animal's brain to produce the freeze lesion. Although hemorrhagic necrosis develops superficially in the cortex after this insult, the underlying white matter exhibits typical vasogenic edema [8].

The animals were imaged at 2, 3, 6, or 24 hr after production of the lesion. The NMR imager has a 0.35 cryogenic magnet; it is the same imager as that previously described in our reports on human clinical material [9]. The SE technique was used with four separate sequences based on changing the interval (TR) between the excitatory radiofrequency (RF) pulses. The four TR intervals were: TR = 500 msec, 1000 msec, 1500 msec, and 2000 msec. The returned signal was sampled at echo delay intervals (TE) of 28 and 56 msec with each RF pulse sequence. The TR determined the number of consecutive sections obtained, which ranged from five to 15, and the data acquisition time, which ranged from 4 to 17 min.

T1, T2 relaxation and mobile proton density values were calculated using the equation: $I = n(H)f(v)(e^{-TE/T_2})(1 - e^{-TR/T_1})$. The reproducibility of calculated values obtained at our institution using this equation has been documented with phantoms and in prior animal studies [10]. Substituting a selected TR value and the two TE values used for any given imaging sequence; sampling the signal intensity (I) in a homogenous region of interest (ROI) on the corresponding images and substituting the values for I; and assuming flow $f(v)$ to be constant, one can solve for the T2 "unknown" in the equation. The T1 unknown can be calculated when a second sequence with a different TR is used. Mobile proton density, $N(H)$, can be calculated using any single TR and TE value from a given sequence. In this manner, T1, T2 relaxation and mobile proton density values were calculated for normal gray and white matter, as well as the edematous white matter subjacent to the lesion, in each animal. Multiple and anatomically consistent samples of normal gray and white matter were analyzed bilaterally in each animal, and the mean value and its standard deviation were recorded for each tissue type. Abnormal white matter, of necessity, could only be sampled in a limited region compared with the normal tissue types. At least 10 pixels and often more were encompassed by each ROI chosen. The good contrast differentiation on the images allowed easy differentiation of normal gray, white, and abnormal white matter, as well as exclusion of obvious cerebrospinal fluid spaces from the ROI.

Those imaging parameters that allowed best delineation of anatomy and depiction of the lesion were identified. After the imaging sequence, each animal was sacrificed and its brain immediately removed. Samples of normal gray, white, and edematous white matter were rapidly selected and analyzed for water content using the wet-to-dry method as well as specific gravity determination. This latter gravimetric technique utilized a bromobenzene-kerosene gradient column [11]. The water content of the various samples was correlated with the calculated T1 and T2 relaxation values obtained.

Results

The images obtained with a TR of 1500 or 2000 msec best showed the normal anatomy of the canine brain, including the differentiation between the gray and the white matter. The edematous white matter was most sensitively detected on the images produced with the second echo sampling, and was seen even on those sequences where TR was less than 1500 msec, for reasons discussed in a previous communication (fig. 1) [12].

The T1 and T2 values were calculated for most permutations of TR and TE parameters available with our imager. The T1 values obtained in the normal gray and white matter of the four animals based on sequences of TR = 500 msec and TR = 2000 msec and their standard deviations are plotted in figure 2. The T2 values obtained with TE = 28 msec and TE = 56 msec during the TR = 1000 msec sequence are plotted in figure 3 (the latter TR value being arbitrarily chosen because it yielded the least standard deviation in the result). Figures 4 and 5 show the plots of T1 and T2 values in the edematous white matter. It should be noted that the absolute values calculated for T1 and T2 relaxation in the normal gray and white matter as well as the abnormal white matter varied as much as 35% in each animal depending on which TR sequences were used for the calculation.

Examination of figures 2–5 reveals that *absolute* T1 and T2 values for normal brain and edematous white matter showed surprising variation from animal to animal. However, the *difference* in T1 or T2 values between normal gray and normal white matter or between normal and edematous white matter showed a more constant relation from animal to animal.

Mobile proton density, $N(H)$, values are shown in table 1. As would be expected in relatively hydrated tissue, $N(H)$ showed an average 28% increase in the edematous white matter and 22% increase in gray matter when compared with normal white matter.

Our initial expectation was that a progressive accumulation of water between the 2 and the 24 hr lesion would result in a corresponding progressive elevation of the T1 and T2 relaxation values in the edematous white matter. However, the water analysis of the brain samples, shown in table 2, revealed a maximal accumulation of water had already occurred in the 2-hr-old lesion, with little change over the subsequent 24 hr period. Hence, not surprisingly, no trend in the T1 or T2 values was demonstrated between the 2- and 24-hr-old lesions. It is of interest that mobile proton density between

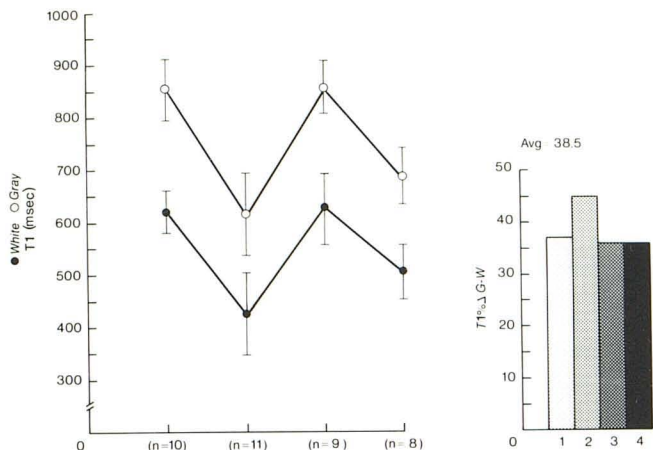


Fig. 2.—Proton imaging (15 MHz). T1 values for normal gray (open circles) and white (solid circles) matter in four animals (n = number of sampled regions in each animal). Bar graph at right shows percentage difference in T1 values between gray and white matter in each animal. Note variation in absolute values of T1 in gray or white matter from animal to animal; however, difference in T1 between gray and white matter in each animal is relatively constant.

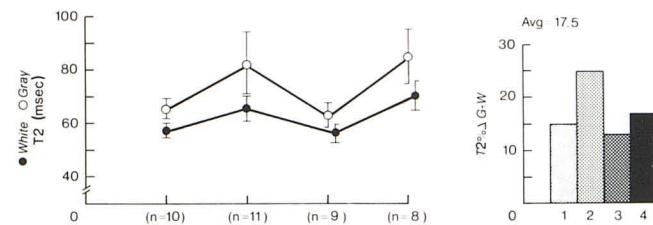


Fig. 3.—Proton imaging (15 MHz). T2 values for normal gray and white matter. Again seen is fluctuation of absolute values from animal to animal, but relative constancy of differences in gray-white matter T2 relaxation, reiterated by bar graph at right.

edematous and normal white matter increased by an average of 28%, while the measured water content (wet-dry ratio) increased an average of 17% (tables 1 and 2).

In summary, NMR imaging proved sensitive to the detection of cerebral edema in addition to showing the normal canine brain anatomy. Calculated T1 and T2 relaxation values and mobile proton density values based on variations of imaging sequence parameters proved useful in defining change within a given animal. However, used in isolation, they were not adequate for comparing normal or edematous brain among different animals, even when the same instrument parameters were used for their calculation.

Discussion

The sensitivity of NMR to edema as well as its ability to separate normal tissues, based at least in part on their different water content, is a welcome attribute of this imaging modality. As shown by this study, the SE technique with long TR intervals can reliably depict alteration of normal white matter composition by vasogenic edema, and separate the

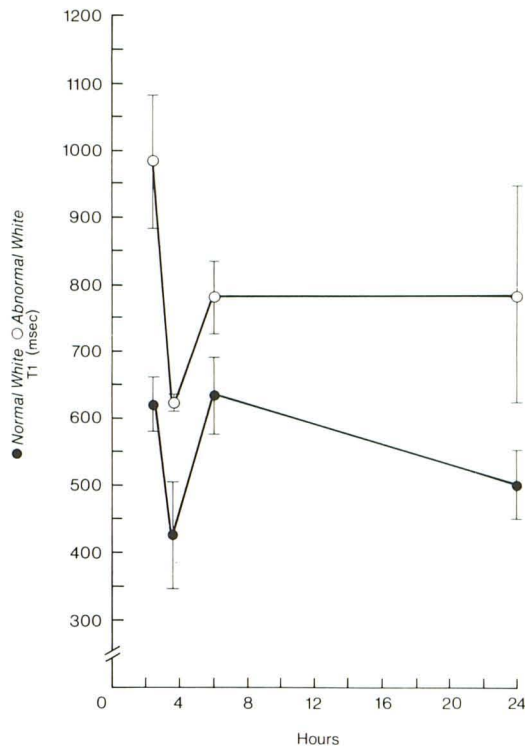


Fig. 4.—Proton imaging (15 MHz). T1 values for edematous (open circles) and normal (solid circles) white matter in each animal plotted in relation to time elapsed from lesion's creation. Note prolongation of T1 in edematous white matter compared with normal white matter in each animal, and relative stability of difference between normal and edematous white matter from animal to animal despite fluctuation of absolute values.

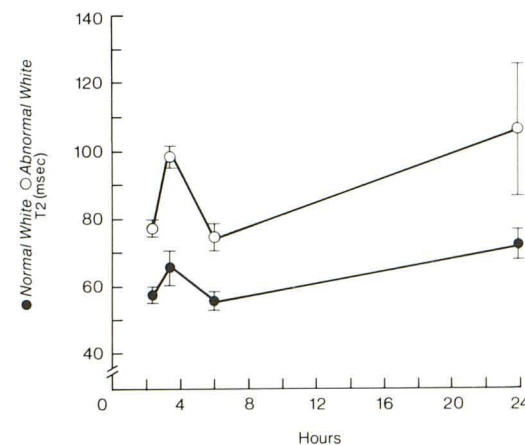


Fig. 5.—Proton imaging (15 MHz). T2 values for edematous (open circles) and normal (solid circles) white matter show prolongation of T2 by edema. Lack of trend between 2 and 24 hr lesion in either T2 or T1 value (fig. 4) plots is from similar water content in all four lesions.

normal white matter from the relatively wetter normal gray matter in any given animal.

It is disturbing to find that calculated T1 and T2 relaxation constants of these three tissue types showed variations in a

TABLE 1: Calculated Mobile Proton Density Values

Brain Matter	Density (H) \pm SD				Average Difference (%)
	Dog 1	Dog 2	Dog 3	Dog 4	
Normal gray	9167 \pm 549	26,844 \pm 2039	8907 \pm 238	20,003 \pm 797	...
Difference (%)	27	22	18	22	22
Normal white	7203 \pm 444	21,927 \pm 2271	7536 \pm 245	16,371 \pm 660	...
Difference (%)	33	29	27	23	28
Abnormal white	9570 \pm 507	28,363 \pm 55	9600 \pm 515	20,074 \pm 1556	...

Note.—Calculations are based on intensity equations, using TR = 2000 and TE = 28 msec.

TABLE 2: Wet-to-Dry and Microgravimetric Analysis (Specific Gravity) of Normal White Matter and Abnormal White Matter in Four Lesions Over Time

	2 hr	3 hr	6 hr	24 hr	Average Difference (%)
% H ₂ O (wet-dry):					
Abnormal white	81.5	83.1	80.3	76.1	...
Difference (%)	18	19	18	15	17
Normal	68.9	69.8	67.8	66.1	...
Specific gravity:					
Abnormal white	1.0340	1.0334	1.0332	1.0296	...
Normal white	1.0424	...	1.0406	1.0432	...

given animal depending on the TR values used to obtain them, and showed variation from animal to animal even when the same TR and TE values were used for the calculation. For example, the T1 of normal white matter in one dog could assume the same value as the T1 of normal gray matter in another dog (fig. 2). Both these observations deserve comment.

The variation of the relaxation time constants with use of different TR values is the subject of current investigation. The intensity equation shows T1 to be an exponential function that may be represented by a curve, while the calculation uses only two variations of TR to "fit" that curve. The accuracy with which T1 can be determined depends on the TR settings used for the pulse sequence employed for its determination. On the basis of the equation, widely spaced TR settings will give more accurate T1 determinations. For this reason, we chose the combination of TR = 500 and TR = 2000 msec for our calculation. Presumably, an even longer TR might provide better accuracy, but would further lengthen study time.

Also, the T2 calculation varied depending on which TR value was chosen for use with the equation. Each of our four TR sequences employs the 28 msec and 56 msec TE values, but the resulting T2 calculation varied depending on which TR value was actually used. We arbitrarily chose to use TR = 1000 for our plots of T2 values because it showed the least standard deviation.

The second problem, that of value variation from one subject to another even with the use of a consistent set of parameters, is potentially more disturbing. All our animals were studied the same day with the same instrument, minimizing methodologic inconsistencies. Like people (but unlike uniformly bred rats or gerbils), mongrel dogs come in different sizes, and perhaps have slightly different states of hydration,

tissue viscosity, and other variables. It may be that this variation of geometry and tissue biochemistry is sufficient to effect a variation in T1 and T2 values of like tissues from subject to subject. Nonuniformity of measurements in different parts of the imaging field is another possible contributor to the variability we observed. Phantom measurements could verify this but, unfortunately, were not done at the time of this study. Most likely, a combination of these factors is responsible for the observed variation, and it is our current challenge to identify them.

These problems illustrate the nonabsolute nature of the relaxation constants as calculated with the NMR imager, and suggest the need for a consistent set of parameters when comparing results between animals. They also serve to illustrate the difficulty of comparing absolute T1 and T2 values in different imagers using different techniques. Somewhat reassuring is the observation that, although the values of a given tissue taken in isolation show fluctuation from subject to subject, disparate tissues in any given subject showed a relatively constant relation to each other, and indeed this relation (for example, between normal gray and normal white matter) was relatively constant in the four different animals. This points out that use of an internal standard might be a way of basing comparisons of T1 and T2 relaxation values among different subjects.

In any given animal, mobile proton density values were predictably elevated in gray matter and edematous white matter when compared with normal white matter, which has a lower concentration of water and its two mobile protons. This, in part, helps explain why the edematous lesion (and gray-white differentiation) was not well seen on the short TR sequences with the first echo images. These are T1-weighted images and might be expected to show the lengthened T1

relaxation in relatively edematous tissue as a region of low intensity, as indicated by the above equation. However, that equation also points out that increased proton density raises intensity and will tend to cancel out the T1 effect in edematous tissue.

It should be stressed that mobile proton density values do not directly correlate with absolute hydrogen concentration in tissue; they merely represent that part of the hydrogen nuclei that is free to participate in the NMR disturbance. For example, although mobile proton density is greater in gray when compared with white matter, absolute hydrogen concentration is the same in both [13]. The role of this tissue parameter in the overall ability to characterize disparate tissues still needs to be explored.

While presenting some difficulties, current SE imaging does sensitively differentiate normal gray, normal white, and edematous white matter in a given animal, consistently shows that increased water content reproducibly prolongs T1 and T2 relaxation in a given animal's tissue, and even provides a basis of comparison between two animals studied under the same conditions, providing an internal standard is used. Future refinements may allow more accurate calculations of T1 and T2 relaxation, calculations unencumbered by our current methodologic difficulties.

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