Commentary

Field-Strength Dependence of Gadolinium Enhancement: Theory and Implications

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The decision to use contrast in magnetic resonance (MR) examination has important diagnostic, economic, and medicolegal implications. The overwhelming majority of published studies defining the clinical utility of gadolinium administration for neuroimaging have been performed at high fields (1–6). Are these conclusions about contrast agent use at high fields equally valid for low-field imaging? Is contrast enhancement at 1.5 T the same as contrast enhancement at 0.15 T?

In this issue of *AJNR*, Chang et al (7) demonstrate convincingly that enhancement depends not only on the MR pulse sequence and dose of contrast administered, but also on the field strength at which the imaging has been performed. Specifically, in their patients with intraaxial brain tumors, the degree of contrast enhancement was significantly greater at 2.0 T than at 0.5 T when the same pulse sequences and doses of gadolinium were used.

The conclusions of this study will come as no surprise to investigators well versed in contrast agent physiology and pharmacology; many of us have long asserted that on theoretical grounds contrast enhancement should vary with field strength. Until now, however, we were able to cite only anecdote and theory in support of this belief. The clinical demonstration of this phenomenon by Chang et al thus serves to justify our theoretical predictions and to bring this issue and its practical implications to the attention of the general radiologist. Further clinical confirmation of the field dependence of gadolinium enhancement also has been provided recently by Prager et al (Prager J, Bower D, Rosenblum J, Huddle D, Ramsey RG, Comparative Enhancement with Gadolinium at High- and Low-Field MR Imaging (abstr), *Radiology* 1993;189(P):241), who reported similar findings and conclusions in 17 patients undergoing cranial imaging at 0.1 T and 1.5 T.

The relatively decreased conspicuity of MR contrast enhancement on low-field images has a sound theoretical basis and follows directly from several well-established biophysical principles (8–10). Nevertheless, the relationship between field strength and contrast enhancement is sufficiently complex that few readers will find it intuitively obvious. In this commentary I will therefore review and further develop the theoretical framework necessary to explain the field dependence of gadolinium enhancement in tissues.

The relaxation properties of tissues are often analyzed using the mathematical model of Zimmerman and Brittin (11), in which tissue components with different magnetic relaxation properties are divided into separate pools or reservoirs, each with its own relaxation rate ($R1_i$). These relaxation rates have units of seconds^{-1} and are merely the reciprocals of the more familiar relaxation times ($T1_i$). In other words, $R1_i = 1/T1_i$. Relaxation *rates* are used instead of relaxation *times* because, under certain conditions described below, the relaxation rates from each pool may be added to calculate the overall relaxation rate of a tissue.

For most tissues, the individual reservoirs are so tightly coupled that a "fast-exchange limit" is assumed to exist. In this situation the spin-lattice relaxation process of the entire tissue can be characterized by a single rate (R1) that is a weighted sum of the intrinsic relaxation rates from each reservoir. For example, if $R1_{pre}$ is the baseline relaxation rate of a tissue without gadolinium and $R1_{Gd}$ is the relaxation rate contribution from the fraction of spins interacting with the gadolinium ion, then the relaxation rate of

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the entire tissue after contrast ($R1_{post}$) can be expressed as:

$$1) \qquad R1_{post} = R1_{pre} + R1_{Gd}$$

The relaxation rate contribution attributable to the gadolinium ion ($R1_{Gd}$) is best understood in terms of the theory developed by Solomon (12) and Bloembergen and Morgan (13). Such analysis shows that the relaxation rate caused by a paramagnetic ion (such as gadolinium) is proportional to the concentration of that ion ([Gd]) and its relaxivity ($X1_{Gd}$). The relaxivity of gadolinium ($X1_{Gd}$) is expressed in units of $[mmol\text{-}s]^{-1}$ and represents the relaxation rate of the gadolinium-containing complex per millimole per liter of solution. In practice, $X1_{Gd}$ is not derived from first principles but is determined empirically by measuring relaxation rates of solutions with different concentrations of the gadolinium ion.

Taken together, the Zimmerman-Brittin and Solomon-Bloembergen-Morgan models provide us with a simplified formulation of the relaxation effects of gadolinium in tissue:

$$2) \qquad R1_{post} = R1_{pre} + [Gd]X1_{Gd}$$

It should be recognized that this expression is based on several assumptions and approximations but is nevertheless sufficiently accurate for the purposes here. By algebraic manipulation of this equation we can derive an expression for the fractional (or percent) change in tissue relaxation rate resulting from contrast administration:

$$3) \qquad \%\ \text{change in } R1 = \frac{R1_{post} - R1_{pre}}{R1_{pre}}$$

$$= \frac{[Gd]X1_{Gd}}{R1_{pre}}(100)$$

This formula shows that the percent change in tissue relaxation rate caused by accumulation of a gadolinium-containing contrast agent is: (*a*) directly proportional to the concentration of that agent; (*b*) directly proportional to the relaxivity of that agent; and (*c*) inversely proportional to the relaxation rate of the tissue before contrast administration.

As we will subsequently demonstrate, both $X1_{Gd}$ and $R1_{pre}$ increase as the resonance frequency decreases. However, $X1_{Gd}$ and $R1_{pre}$ do not scale proportionally with field strength, and it is this disparity in their frequency dependence that accounts for the differences in contrast enhancement between low-field and high-field MR. The physical mechanisms accounting for the field dependence of $X1_{Gd}$ and $R1_{pre}$ are far beyond the scope of this paper, and the interested reader is therefore referred to several more advanced treatises (8, 9, 14–16). Notwithstanding these more sophisticated analyses, the field dependence of biological tissues remains so poorly understood that we must ultimately rely on empiric measurements of their field dependence obtained in a special laboratory MR instrument known as a *field-cycling relaxometer.*

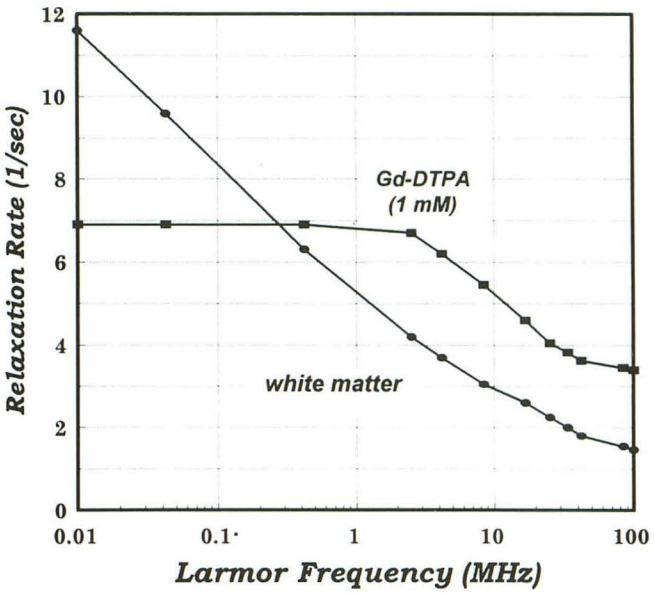

Fig 1. A nuclear magnetic resonance dispersion (NMRD) curve showing the frequency dependence of relaxation rates of white matter and a 1-mmol/L aqueous solution of gadopentetate dimeglumine (*Gd-DTPA*). Note that below about 2 to 3 MHz, the relaxation rate of gadopentetate dimeglumine is relatively constant, whereas the relaxation rate of white matter continues to increase. (Data obtained from References 15–17.)

The data obtained from relaxometry experiments are usually displayed in a graph form as a nuclear magnetic resonance dispersion (NMRD) curve. The horizontal axis of the NMRD graph is typically the logarithm of field strength or resonance frequency, and the vertical axis is the relaxation rate or relaxation potential of the substance being measured.

Figure 1 demonstrates the NMRD curves for white matter and a solution of 1 mmol/L gadopentetate dimeglumine based on previously published data (14–16). Note that the relaxation rates of both white matter and gado-

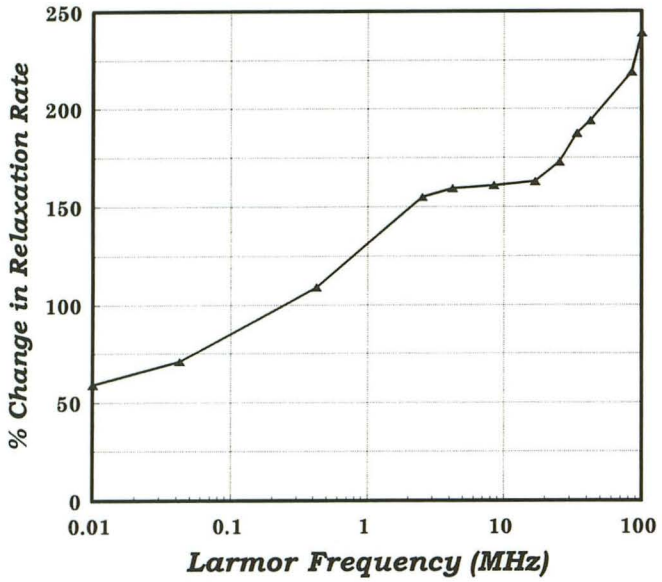

Fig 2. Percent change in T1 relaxation rate of white matter that contains 1 mmol/L of gadopentetate dimeglumine. Because the relaxation rates of gadopentetate dimeglumine and of white matter do not scale proportionally with frequency, the curve is nonlinear. The greatest nonlinearity is noted between 20 and 100 MHz, corresponding to field strengths in the range of conventional MR (ie, approximately 0.5 to 2.3 T). (Data obtained from References 15–17, transformed by Equation 3.)

pentetate dimeglumine increase as field strength (Larmor frequency) decreases. Furthermore, this field dependence is highly nonlinear and substance specific—the relaxation rate of white matter changes much more rapidly than that of gadolinium, particularly at low fields. In other words, as field strength decreases the R1 of white matter increases proportionally more than the R1 of gadolinium. Below about 4 MHz (0.1 T) the relaxation rate of gadolinium "plateaus," whereas the relaxation rate of white matter continues to increase.

The effect on overall relaxation rate can be better appreciated in Figure 2, which displays the percent change in relaxation rate of white matter containing 1 mmol/L gadopentetate dimeglumine as a function of resonance frequency. As can be seen from this graph, gadolinium induces a relatively greater fractional change in white matter relaxation rate at high fields than low fields. This relationship is nonlinear and nonintuitive but clear. Through a long process involving biophysical models, equations, and empirically obtained nuclear MR dispersion curves, we have finally demonstrated that the clinical observations of Chang et al and Prager et al have a theoretical justification—contrast enhancement *is* dependent on field strength.

The practical applications of these findings are immediate and significant. First, all users of low-field instruments should recognize that *contrast enhancement of certain cerebral lesions may not be as vivid on the low-field images as on those obtained using identical parameters and contrast dose at high field.* A real possibility therefore exists that one might underestimate the size, margins, or character of a lesion if one bases this judgment solely on the enhancement properties seen at low field. Furthermore, some lesions that enhance only weakly at high field may appear not to enhance at all on low-field images. For example, a very small metastasis with weak enhancement might be missed on a standard-dose, low-field MR study. Additionally, changes in the degree of contrast enhancement on follow-up imaging may not be a reliable indicator of biological behavior or response to therapy if the scans used for comparison have been performed at different field strengths.

A second important caveat derived from the study of Chang et al is that *users of low-field instruments always should endeavor to use postcontrast pulse sequences that are as T1 weighted as possible.* Further research needs to be directed toward developing new sequences to improve the detection of gadolinium enhancement on low-field instruments. Such techniques might include fast spin-echo inversion recovery imaging (17), magnetization-prepared spoiled gradient-echo imaging (18), large-tip-angle spin-echo imaging (19), or magnetization transfer saturation (20).

Finally, serious consideration and dedicated clinical trials may be indicated involving the use of double- or triple-dose contrast for low-field imaging. The additional diagnostic utility of triple-dose contrast, already promising for certain high-field applications (21, 22), may be even more dramatic at low fields. At a minimum, users of low-field MR scanners who routinely give less than the standard (0.1 mmol/kg) dose of gadolinium contrast should reconsider this practice seriously in light of the findings presented here.

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