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How much contrast is enough?

Dependence of enhancement on field strength and MR pulse sequence

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Abstract. The overwhelming majority of published studies defining the clinical utility of gadolinium administration for neuroimaging have been performed at high field using conventional spin-echo imaging. Concerning the issue of field strength, several investigations have now shown that for a given dose of contrast, enhancement is less apparent at low field than at high field. Concerning the issue of pulse sequence, there is now convincing clinical and experimental evidence that all T1-weighted sequences are not equal in demonstrating contrast enhancement. Specifically, T1-weighted spoiled gradient-echo sequences do not show the same degree of visually apparent contrast enhancement compared to conventional spin-echo sequences. The use of magnetization transfer techniques which demonstrate areas of enhancement unseen on conventional pulse sequences is also addressed.

Key words: Magnetic resonance imaging – Field strength – Contrast media, dose – Gadolinium, diagnostic use

Introduction

The decision to use an MR contrast agent, and if so at what dose, 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-field using conventional spin-echo imaging. Are the conclusions from these studies universally applicable to all MR systems? Is contrast enhancement at 1.5 T the same as contrast enhancement at 0.15 T? Does it matter whether one uses a T1-weighted spin-echo or gradient echo sequence? How does the adjunctive use of magnetization transfer saturation pulses affect these conclusions?

Field strength dependency of gadolinium enhancement

The relatively decreased conspicuity of MR contrast enhancement on low-field (compared to high-field) images has a sound theoretical basis and follows directly from well-established biophysical principles [1–3]. Furthermore, several clinical studies [4–6] have now convincingly demonstrated this phenomenon in vivo. Nevertheless, the relationship between field strength and contrast enhancement is sufficiently complex that few readers will find it intuitively obvious [7]. In this section I will 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 [8], in which tissue components with different magnetic relaxation properties are divided into separate pools or reservoirs, each with its own relaxation rate ($R1_i = 1/T1_i$). According to "fast-exchange theory", 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 the entire tissue postcontrast ($R1_{post}$) can be written

$$R1_{post} = R1_{pre} + R1_{Gd}$$

According to theory developed by Solomon, Bloembergen, and Morgan [9, 10], the relaxation rate contribution due to the gadolinium ion ($R1_{Gd}$) is proportional to the tissue concentration of gadolinium ([Gd]) multiplied by its relaxivity ($r1_{Gd}$). The relaxivity of gadolinium ($r1_{Gd}$) is expressed in units of $[mM\text{-}sec]^{-1}$ and represents the relaxation rate of the gadolinium-containing complex per millimole per liter of solution. In practice, $r1_{Gd}$ 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:

$$R1_{post} = R1_{pre} + [Gd] \cdot r\,1_{Gd}$$

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:

$$\%Change\ in\ R1 = \frac{R1_{post} - R1_{pre}}{R1_{pre}} = \frac{[Gd] \cdot r1_{Gd}}{R1_{pre}}$$

This formula shows us that the percent change in tissue relaxation rate due to accumulation of a gadolinium-containing contrast agent is (1) directly proportional to the concentration of that agent, (2) directly proportional to the relaxivity of that agent, and (3) inversely proportional to the relaxation rate of the tissue prior to contrast administration.

Both $r1_{Gd}$ and $R1_{pre}$ increase nonlinearly and disparately as the resonance frequency decreases [1, 2, 11–13]. The frequency dependence of $r1_{Gd}$ and $R1_{pre}$ can be measured in a special laboratory NMR instrument known as a field-cycling relaxometer. The data obtained from such relaxometry experiments is usually displayed in a graphical form known 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 relaxivity of the substance being measured.

Figure 1 demonstrates the NMRD curves for white matter and a solution of 1 mM Gd-DTPA based on previously published data [11–13]. Note that the relaxation rate of white matter changes much more rapidly than that of gadolinium, particularly at low fields. 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 mM Gd-DTPA 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 quite clear.

To summarize the underlying theory: (1) The T1 relaxation time of brain is dependent on field strength; (2) The relaxivity of gadolinium also depends on field strength, but in a fashion differing from that of brain; (3) The relaxation time of {gadolinium + brain} is a nonlinear function of field strength, with a fractionally greater effect at high field than at low field.

Several clinical studies can also be cited in support of these theoretical observations. Lindsey et al. [4] demonstrated that normally enhancing intracranial tissues like the cavernous sinuses were relatively less intense compared to brain at 0.5 T than at 1.5 T (Fig. 3). Chang and

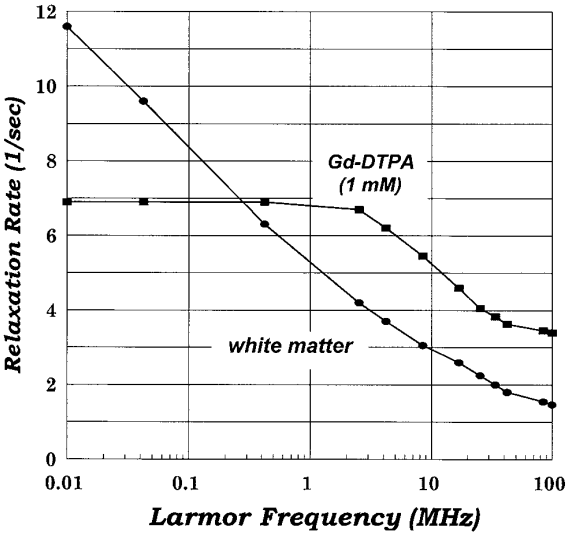

Fig. 1. Nuclear magnetic resonance dispersion (NMRD) curve showing the field dependence of relaxation rate (1/T1) for white matter and a 1 mM solution of Gd-DTPA. Note the different shapes of the two curves relating to different molecular relaxation mechanisms at different field strengths

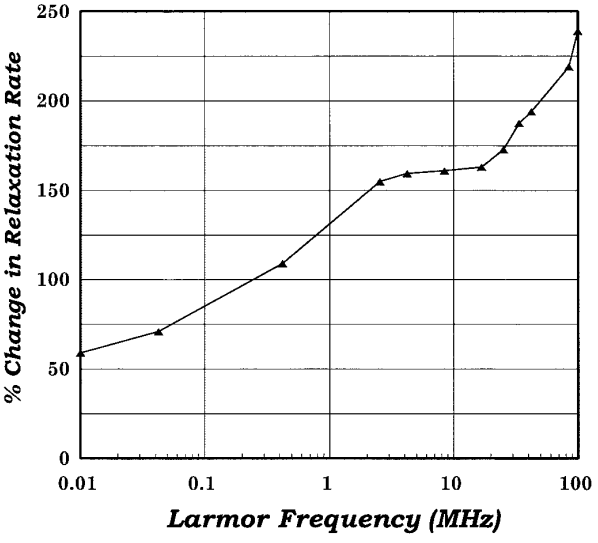

Fig. 2. Percent change in T1 relaxation rate of white matter that contains 1 mM of Gd-DTPA. Because of the relaxation rates of Gd-DTPA and white matter do not scale proportionally with frequency, the curve is nonlinear. The greatest nonlinearity is noted between 20 and 100 MHz, corresponding to field strengths in the range of conventional MR imaging (i.e., approximately 0.5–2.3 T)

colleagues [5] recently compared contrast enhancement in 31 patients with brain tumors as a function of dose and field strength (Fig. 4). For both single-dose and double-dose studies, the lesion-to-brain contrast-to-noise ratios were nearly a factor of two higher at 2.0 T than at 0.5 T. Similar conclusions were also drawn by Prager et al. [6], who measured enhancing cranial lesions at 0.1 T, 0.3 T, and 1.5 T.

The practical applications of these findings are immediate and significant. First, all users of low-field instruments should recognize that contrast enhancement

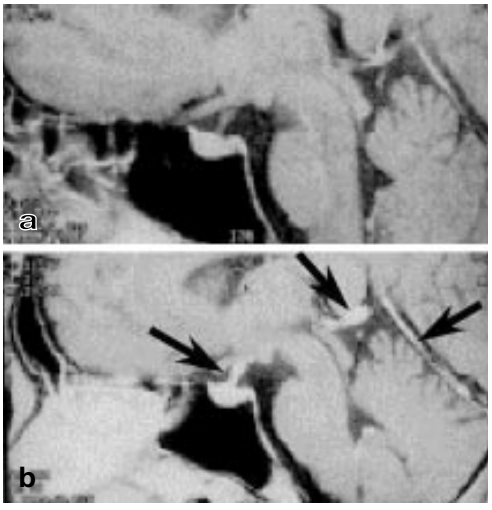

Fig. 3. Sagittal postcontrast images of the brain at **a** 0.5 T and **b** 1.5 T. Note the relative increased enhancement of the pituitary stalk, pineal, and dural sinuses on the high-field image. (Reprinted from [4] with permission)

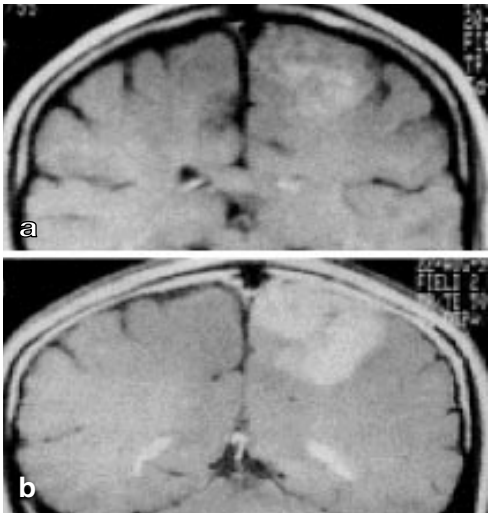

Fig. 4. Coronal postcontrast images of a brain tumor at **a** 0.5 T and **b** 2.0 T. Note the more intense contrast enhancement at high field. (Reprinted from [5] with permission)

of certain cerebral lesions may not be as vivid on the low-field images as 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 potentially 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 biologic behavior or response to therapy if the scans used for comparison have been performed at different field strengths.

A second important caveat is that users of low-field instruments should always 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 [14], magnetization-prepared spoiled gradient-echo imaging [15], large tip-angle spin-echo imaging [16], or magnetization transfer saturation [17].

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 shown promising for certain high-field applications [18, 19], 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 seriously reconsider this practice in light of the findings presented here.

MR pulse sequence and gadolinium enhancement

The overwhelming majority of MR papers dealing with contrast enhancement have utilized conventional T1-weighted (i.e., short TR/short TE) sequences for imaging. Although almost universally employed for clinical MR imaging, there is no proof that these standard sequences are in any manner optimal (or even adequate) for the visualization of contrast enhancement. Even within the subset of "T1-weighted spin-echo imaging" considerable variability in protocols exists from site to site as a function of hardware, field strength, and personal preferences. For example, routine postcontrast brain imaging may be done with a 5-mm-thick SE 600/20 technique at one center and a 4-mm-thick SE 500/15 sequence at another center. Are these two techniques fully equivalent for the detection of contrast-enhancing lesions?

Although it is difficult to determine subtle differences between T1-weighted spin-echo techniques, there is now convincing clinical and experimental evidence that T1-weighted spoiled gradient echo (SPGR) sequences do not show contrast enhancement as well as spin-echo sequences (Fig. 5). Chappell et al. [20] found this to be true especially for small lesions (such as metastases and multiple sclerosis plaques) without much surrounding edema. The biophysical basis of this phenomenon was studied by Rand et al. [21] who found that the decreased sensitivity of gradient echo sequences to MR contrast enhancement was principally due to the short TR values used in such sequences.

Do all T1-weighted gradient echo sequences suffer from this defect? For example, are magnetization-prepared gradient echo sequences (like MP-RAGE) better than SPGR at revealing contrast enhancement? The answer is not yet known. Although SPGR sequences appear inferior for the detection of contrast enhancement, magnetization transfer techniques appear superior to conventional spin-echo imaging.

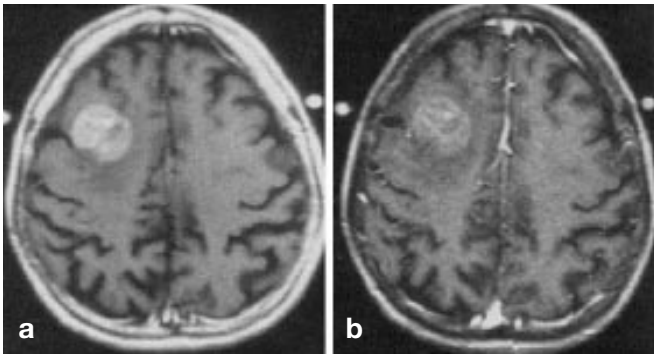

Fig. 5. A brain tumor seen after contrast administration using **a** conventional spin echo imaging (SE 600/10) and **b** a spoiled gradient echo technique (SPGR 35/5/45°). Note the decreased visualization of contrast enhancment in **b**. (Reprinted from [21] with permission)

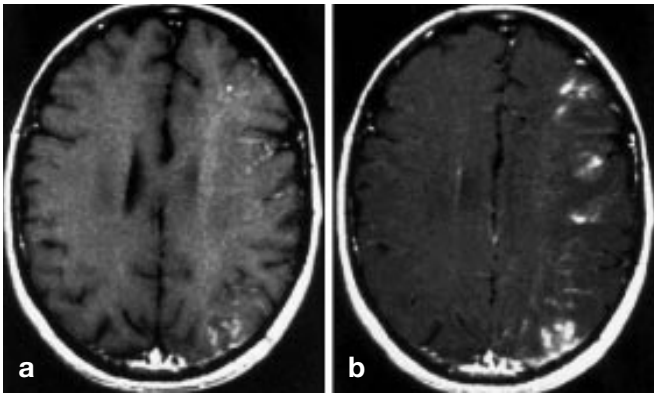

Fig. 6. A 65-year-old man with a recent left hemisphere cerebral infarction. **a** Conventional postcontrast T1-weighted image reveals weak parenchymal enhancement over the left middle cerebral artery territory. **b** MT-enhanced image shows more extensive contrast enhancement in the same area

Magnetization transfer (MT) imaging is a relatively new MR technique in which image contrast is modulated by selectively saturating a pool of tightly coupled protons in macromolecules and their associated "bound" water in their hydration layers [22–25]. Although many variations of this method exist [26], the usual MT technique consists of applying a presaturation pulse with center frequency shifted from the water resonance by several hundred to several thousand Hertz. This off-resonance pulse has sufficient power to saturate protons in the macromolecular pool without directly affecting those in free water. After the MT saturation pulse has been applied, a routine MR imaging sequence (e.g., spin echo, gradient echo) can then be performed. MT saturation of the pool of macromolecular protons is transferred to nearby water molecules, presumably by means of dipolar cross-coupling and chemical exchange interactions [27]. Through these complex interactions, tissue relaxation parameters are altered and new image contrasts may be revealed [23]. At frequency offsets below 2000 Hz, Ulmer et al. [28] and Moran and Hamilton [29] have recently shown that spin-lock relaxation phenomena sensitive to tissue T1/T2 ratios also contribute to MR signal characteristics during MT saturation.

Although the precise mechanisms underlying the MT phenomenon are incompletely understood, there is general agreement that the central effect of MT pulses is to reduce signal from tissues rich in macromolecules, particularly those containing relatively large numbers of hydrogen nuclei incorporated into cell membranes, phospholipids, enzymes, and proteins. Gadolinium enhancement, acting principally through a direct water – Gd^{+} 3 ion interaction not mediated by macromolecules, is relatively unaffected by the MT pulse. As such, the degree of visible contrast enhancement is increased 2–3 fold, depending on the disease process and dose of contrast employed (Fig. 6).

Conclusions

How much contrast is enough? The answer clearly depends not only on the disease process, but on other technical factors including field strength and MR pulse sequence. In spite of their importance, the field strength and pulse sequence dependency of contrast enhancement has been relatively slighted in the medical literature. Perhaps the most provocative and disturbing realization is that no gold standard exists concerning what constitutes optimal (or even adequate) visualization of contrast enhancement. Recent work with magnetization transfer and high dose contrast in a variety of disease states shows that it is possible to identify subtle areas of blood-brain barrier disruption beyond that seen on conventional studies [17]. To what extent we can push the limits of contrast agent detection will remain an active research topic for years to come.

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