Published in final edited form as:

Magn Reson Med. 2013 April ; 69(4): 1104–1108. doi:10.1002/mrm.24331.

ΔR_2^* Gd-DTPA relaxivity in venous blood

Vishal Patil and Glyn Johnson

Center for Biomedical Imaging, Department of Radiology, New York University School of Medicine, 660 First Avenue, New York, NY 10016

Abstract

The accuracy of perfusion measurements using dynamic susceptibility contrast (DSC) MRI depends on estimating contrast agent concentration in an artery, i.e., the arterial input function (AIF). One of the difficulties associated with obtaining an AIF are partial volume effects (PVEs) when both blood and brain parenchyma occupy the same pixel. Previous studies have attempted to correct AIFs which suffer from PVEs using contrast concentration in venous blood. However, the relationship between relaxation and concentration (C) in venous blood has not been determined *in vivo*. In this note a previously employed fitting approach is used to determine venous relaxivity *in vivo*. *In vivo* relaxivity is compared to venous relaxivity measured *in vitro* in bulk blood. The results show that the fitting approach produces relaxivity calibration curves which give excellent agreement with arterial measurements.

Keywords

Relaxivity; venous; DSC MRI; perfusion

Introduction

Relaxivity, the relationship between relaxation rate (R_2^*) and tracer concentration (C), is an important function in every DSC MRI analysis. It is normally assumed that the relaxivity of paramagnetic tracers such as Gadolinium-diethylenetriaminepentaacetic acid, (Gd-DTPA) is linear; however this is only true in simple solutions. In tissues – both brain parenchyma and blood – the relationship is distinctly non-linear due to secondary magnetic field perturbations created by the tissue microenvironment (1–5). Studies have shown neglecting the non-linear nature of relaxivity *in vivo* substantially affects the accuracy of perfusion measurements such as cerebral blood volume and flow (6).

The arterial input function (AIF, i.e., the concentration of tracer in arteries) is generally used in DSC measurements and the relaxivity of Gd in arterial blood has been well characterized empirically (4,7). Measurements of *venous* concentration can be used to automate arterial pixel selection and correct for partial volume effects in the AIF (8–10). These methods have assumed that the relaxivity of arterial and venous blood are the same. However, this is not generally the case as the presence of paramagnetic deoxyhemoglobin in will contribute to venous relaxivity. A recent study by Blockley et al. empirically determined the relaxivity of venous blood *in vitro* at different field strengths using a blood phantom doped with a Gd based tracer (5). This study found that relaxivity was quadratic with the minimum at some positive value of Gd concentration, C , i.e., that relaxivity initially *decreases* with increasing C , as the presence of paramagnetic Gd decreases field differences between diamagnetic

plasma and paramagnetic deoxygenated red blood cells. This would result in an increase in signal intensity at the beginning of the bolus but this behavior does not appear to be observable *in vivo*.

The aim of this note is therefore to determine the relaxivity of venous blood by a fitting approach previously used to determine brain parenchyma relaxivity (11). The approach determines the quadratic venous relaxivity function that gives the best agreement between the areas under arterial and venous concentration-time curves (CTCs).

Methods

Imaging Parameters

The study was approved by the Institutional Review Board of this institution. DSC data was acquired from 6 meningioma subjects at 1.5T (TR 1s; TE 47ms; FA 40°; matrix 128×128; FOV 228×228 mm²; 7×5mm slices) and 3T (TR 1s; TE 32ms; FA 30°; matrix 128×128; FOV 230×230 mm²; 10×5mm slices) using a gradient echo EPI sequence during injection of 0.1mmol/kg Gd-DTPA.

Signal Measurements

Arterial and venous pixels are detected semi-automatically using adaptations of techniques first suggested by Rempp et al. (12). First, signal was averaged over all images at each time point to obtain an average brain signal. Although it might be preferable to extract the brain first, in practice this average is dominated by brain pixels. The following parameters are then measured: fractional signal drop (FSD), full width at half drop (FWHD) and arrival time (AT, defined as the time at which signal is decreased by 10% of the maximum FSD). Candidate arterial pixels were defined as those with a FWHD at least 1s less than the average brain value and an AT at least 1 second before the average brain value. Similarly candidate venous pixels were defined as those 1s wider and 1s later than the average. Candidate pixels were visually inspected and the ten with the greatest FSD that showed no evidence of “spiky” boluses, indicative of phase cancellation with surrounding parenchymal pixels (4), were averaged to produce arterial and venous measurements for each patient.

Signal in an EPI sequences (neglecting T_I effects) is given by

$$S = S_{pre} \exp(\Lambda(0) - \Lambda(C)) \quad [1]$$

where S_{pre} is the pre-bolus signal and Λ is a function of concentration. The relaxivity of arterial bulk blood has been measured empirically at multiple field strengths and has been found to follow a quadratic

$$\Lambda(C) = (qC^2 + pC) T_E \quad [2]$$

At 1.5T, $q = 0.74 \text{ s}^{-1} \text{mM}^{-2}$ and $p = 7.62 \text{ s}^{-1} \text{mM}^{-1}$ (4); at 3T, $q = 2.61 \text{ s}^{-1} \text{mM}^{-2}$ and $p = 0.5 \text{ s}^{-1} \text{mM}^{-1}$ (7). (Hematocrit was 40% in both cases.)

The *in vitro* relaxivity of venous bulk blood with a 30% oxygen extraction fraction (OEF) follows a parabola but with a shift $0(a)$ along the concentration axis

$$\Lambda(C) = (q(C-a)^2 + pC) T_E \quad [3]$$

At 1.5T, $q = 6 \text{ s}^{-1}\text{mM}^{-2}$, $p = -11 \text{ s}^{-1}\text{mM}^{-1}$ and $a = -0.046 \text{ mM}$; 3T, $q = 18 \text{ s}^{-1}\text{mM}^{-2}$, $p = -35 \text{ s}^{-1}\text{mM}^{-1}$ and $a = 0.037 \text{ mM}$ (hematocrit 42%) (5).

In this study we assumed the same form for relaxivity as found in bulk blood, Eq. [3], but found the parameters q , p and a that gave the best agreement between arterial and venous CTCs by the following fitting procedure similar to that used previously used to determine parenchymal relaxivity (11).

Fitting Method

All CTCs were fitted to the single compartment recirculation (SCR) model (13)

$$C(t) = g(t) + \kappa \int_0^t g(\tau) d\tau \quad [4]$$

where κ is a ratio of the area under the bolus to the recirculation height of the curve and is a constant less than one (usually about 0.05) and g is the gamma variate function

$$g(t; y_{\max}, t_{\max}, \alpha) = y_{\max} t'^{\alpha} \exp(\alpha(1-t')) \quad [5]$$

where

$$t' = \frac{(t-t_0)}{t_{\max}-t_0}, \quad [6]$$

t_0 is the start of the bolus, $t_{\max}$ is the time when the bolus is at maximum height, $y_{\max}$ is the maximum height and α is a decay parameter. The first term in Eq. [4] (the gamma variate) describes the tracer bolus *per se* so that the area under the curve is given by

$$A = \int g(t) dt = y_{\max} \left(\frac{t_{\max}}{\alpha} \right)^{\alpha+1} \Gamma(\alpha+1) \quad [7]$$

where Γ is the gamma function. The integral term describes recirculating contrast. The SCR model is preferable to the alternative of fitting a gamma variate to the bolus portion of the CTC alone for a number of reasons (13).

The procedure is based on the basic postulates of DSC MRI that 1) the area under the bolus, A , must be equal for arterial and venous (and all other vascular) CTCs and 2) the height of the recirculation portion of the CTCs must also be equal. The values of q , p and a that best realize these conditions were found by simultaneously fitting CTCs from 5 patients at both 1.5 and 3T. Briefly, for each patient A and κ are estimated in the artery by modeling the CTC as Eq. [4], converting to signal using Eq. [1] and the bulk arterial blood relaxivity curves (Eq. [2]) and fitting to the measured signal with S_0 , $y_{\max}$, t_0 , $t_{\max}$, α and κ as free parameters. Similarly each vascular CTC is modeled by Eq. [4], converted to signal using Eqs. [1] and [3] and fitted to the measured signal. However, the venous fit is constrained to give equal values of A (Eq. [7]) (and hence $y_{\max}$) and κ to those found in the artery but with the relaxivity parameters q , p and a as fitting parameters in addition to S_0 , t_0 , $t_{\max}$ and α . Fits to all 5 patients were performed simultaneously with different gamma variate parameters for each patient but the same relaxivity parameters for all. Since we are comparing two pools of blood with the same hematocrit, it is not necessary to correct for this. Fitting to signal rather than estimates of concentration avoids errors associated with the non-linear relationship

between noise and concentration (14–15). Including S_0 as a fitting parameter is somewhat unusual but should provide the best overall fit of the data.

Results

Figure 1 shows measured (points) and fitted (line) venous signal measurements for 5 patients at 1.5 (a) and 3T (b). Table 1 gives the coefficients for venous relaxivity (Eq. [3]) derived from *in vivo* fitting. It should be noted the a term is very small and can in practice be neglected. This finding is in contrast to that in *in vitro* bulk blood (5) measurements. Figure 2 shows relaxivity calibration curves for arterial (red) blood, *in vitro* bulk venous blood (5) (black; coefficients are given in the methods section) and *in vivo* venous blood (blue) at 1.5 (a) and 3T (b).

Figure 3 shows CTCs derived for arterial signals (red), and venous signals using *in vitro* bulk blood relaxivity (black) and *in vivo* venous relaxivity expressions (blue) at 1.5 (a) and 3T (b). (The discontinuities in the *in vitro* curves are due to the ambiguity in relaxivity estimation caused by the non-monotonic nature of the *in vitro* relaxivity curve. Values between zero concentration and the first non-ambiguous concentration have therefore been derived by interpolation.) With the *in vivo* relaxivity, the relative widths, heights and arrival times of the arterial and venous curves are consistent with what would be expected from delay and dispersion: the arterial bolus starts before and is narrower and higher than the venous, the recirculation portion of the curve is of similar height. The venous CTC derived by the *in vitro* calibration curves are in very poor agreement with what would be expected from the arterial curves. The recirculation portion of the curve is grossly overestimated at both fields; at 1.5T the bolus is both higher peak and broader than the arterial curve which is not physiologically feasible.

Discussion

Theoretical modeling of Gd relaxivity in blood is a difficult problem and, as far as we are aware, has not yet proved amenable to analysis. Relaxivity expressions have therefore been found empirically using phantoms and been shown to resemble a quadratic for both arterial and venous blood. In this study we therefore empirically determined the quadratic function that best describes relaxivity in *in vivo* venous blood at 1.5 and 3T. The excellent fits in Fig. 1 confirm that quadratic functions adequately describe venous relaxivity although they do not prove that this is the true functional form. The agreement between arterial and venous CTCs derived from the *in vivo* relaxivity expressions (Fig. 3) further confirm this.

The quadratic term in the 1.5T *in vivo* relaxivity expression is very small, unlike that in other measurements. Again, theoretical modeling is difficult and we have no good explanation for this finding. However, we do note that similar findings are seen in arterial measurements.

The *in vitro* relaxivity curves (Fig. 2) give negative ΔR_2^* over a critical range of concentrations that include those seen during recirculation (between 0.5 and 1 mM – Fig. 3). If the arterially derived concentrations are correct the *in vitro* curves would predict a distinct signal increase at the beginning of the bolus and a recirculation portion greater than S_{pre} . Neither of these are seen in any venous measurements (Fig. 1).

Relaxivity is largely determined by magnetic field inhomogeneities caused by susceptibility differences between diamagnetic plasma, paramagnetic deoxyhemoglobin confined to the red blood cells (RBCs), paramagnetic contrast agent within the plasma and the diamagnetic surroundings (tissue *in vivo*, air or water *in vitro*). In large phantoms, inhomogeneities will be dominated by differences between plasma and RBCs. As the concentration of contrast

agent increases these inhomogeneities will initially decrease until the susceptibility of the plasma equals that of the RBCs, creating a minimum in the relaxivity curve shifted to the right along the concentration axis. In small vessels, however, susceptibility differences between the lumen and surrounding tissue will also contribute to inhomogeneity and hence relaxivity. The initial dose of contrast agent will increase these inhomogeneities thus potentially negating the effect of RBC/plasma differences. This could explain the discrepancy between *in vitro* and *in vivo* relaxivities. If this explanation is correct it suggests that the relaxivity parameters derived here will be somewhat dependent of vascular diameter and should therefore be used with caution in veins different in size from cerebral veins. (Note that this effect would have less effect on *in vitro* measurements of arterial blood since oxygenated RBCs are diamagnetic.)

DSC data must be acquired with sufficient temporal resolution to capture the passage of the bolus so relatively low spatial resolution acquisitions are employed. Blood vessels are therefore likely to be smaller than the dimensions of pixels so that vascular measurements are contaminated by partial volume effects (PVEs). PVEs can result in phase cancellation of signal between vessels and surrounding tissue (17–18). Such phase errors can introduce distortions in bolus shape and errors into the calibration. These errors also usually cause characteristically “spikey” and square signal drops that approach zero. For this reason we visually inspected the candidate arterial and venous curves and rejected those showing these effects. PVEs can also cause reductions in signal drops. However, our method is partially resistant to such errors for the following reason. The calibration is based both on a comparison of bolus area, A , and κ which is the ratio of post bolus concentration to A . Essentially κ is a ratio of concentrations since A is the integral of concentrations. If C is reduced by a factor α due to partial volume effects then the estimate of C is

$$\widehat{C} = \Lambda^{-1}(\Lambda(\alpha C))$$

where Λ^{-1} is the inverse of Λ , i.e., the calibration function that we are seeking, and we have assumed $T_E = 1$ for simplicity. If Λ^{-1} is incorrect then

$$\widehat{C} = \alpha C + \varepsilon(C)$$

where ε is an error term, which is dependent on C because Λ is non-linear. Because of this

$$\frac{\widehat{C}_1}{\widehat{C}_2} \neq \frac{C_1}{C_2}.$$

Thus, if partial volume effects are substantial and if our calibration function is incorrect it will introduce large errors between measured and fitted curves in Figure 1.

There are a number of limitations to this study: First, we took no account of T_1 saturation effects. However, with our sequence parameters saturation should be only 13% and we saw no evidence of any effects such as an initial or post bolus increases in signal intensity. Second, hematocrit and OEF will influence relaxivity (15) so that large variations in these parameters will reduce the accuracy of our calibration values. However, a previous study by Akbudak et al. demonstrates that provided *plasma* concentrations are compared hematocrits

between 30% and 40% do not produce large differences in R_2^* within the range of concentration in which we are interested (0 – 5 mM) (7). Since hematocrit is equal in arteries and veins any effects will tend to cancel out. Thirdly, the *in vitro* experiments used ProHance as a gadolinium chelate, not Gd-DTPA. This may explain some of the discrepancies though there appears to be little evidence in the literature to suggest major relaxivity differences between most contrast agents. Lastly, the *in vitro* relaxivity curve was determined over a smaller range of concentrations than the *in vivo* so that the latter may be more reliable at high concentrations.

Acknowledgments

This study was funded in part by NIH grant R01CA111996.

References

1. Kennan RP, Zhong J, Gore JC. Intravascular susceptibility contrast mechanisms in tissues. *Magn Reson Med*. 1994; 31(1):9–21. [PubMed: 8121277]
2. Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM. MR contrast due to intravascular magnetic susceptibility perturbations. *Magn Reson Med*. 1995; 34(4):555–566. [PubMed: 8524024]
3. Kiselev VG. On the theoretical basis of perfusion measurements by dynamic susceptibility contrast MRI. *Magn Reson Med*. 2001; 46(6):1113–1122. [PubMed: 11746577]
4. van Osch MJ, Vonken EJ, Viergever MA, van der Grond J, Bakker CJ. Measuring the arterial input function with gradient echo sequences. *Magn Reson Med*. 2003; 49(6):1067–1076. [PubMed: 12768585]
5. Blockley NP, Jiang L, Gardener AG, Ludman CN, Francis ST, Gowland PA. Field strength dependence of R_1 and R_2^* relaxivities of human whole blood to ProHance, Vasovist, and deoxyhemoglobin. *Magn Reson Med*. 2008; 60(6):1313–1320. [PubMed: 19030165]
6. Calamante F, Connelly A, van Osch MJ. Nonlinear Delta R_2^* effects in perfusion quantification using bolus-tracking MRI. *Magn Reson Med*. 2009; 61(2):486–492. [PubMed: 19161169]
7. Akbudak, E.; Kotys, MS.; Memisevic, D.; Conturo, TE. Quadraticity and hematocrit dependence of ΔR_2^* AIF signals at 3T: a blood phantom study under physiological conditions. Syllabus of the ISMRM workshop on Quantitative Cerebral Perfusion Imaging Using MRI: A Technical Perspective; Venice. 2004. p. 10-11.
8. Knutsson L, Borjesson S, Larsson EM, Risberg J, Gustafson L, Passant U, Stahlberg F, Wirestam R. Absolute quantification of cerebral blood flow in normal volunteers: correlation between Xe-133 SPECT and dynamic susceptibility contrast MRI. *J Magn Reson Imaging*. 2007; 26(4):913–920. [PubMed: 17896379]
9. Zaharchuk G, Bammer R, Straka M, Newbould RD, Rosenberg J, Olivot JM, Mlynash M, Lansberg MG, Schwartz NE, Marks MM, Albers GW, Moseley ME. Improving dynamic susceptibility contrast MRI measurement of quantitative cerebral blood flow using corrections for partial volume and nonlinear contrast relaxivity: A xenon computed tomographic comparative study. *J Magn Reson Imaging*. 2009; 30(4):743–752. [PubMed: 19787719]
10. Bjornerud A, Emblem KE. A fully automated method for quantitative cerebral hemodynamic analysis using DSC-MRI. *J Cereb Blood Flow Metab*. 2010; 30(5):1066–1078. [PubMed: 20087370]
11. Patil, V.; Jensen, JH.; Johnson, G. Direct Measurement of Arterial Input Function in White Matter. Proceedings of ISMRM 18th Annual Meeting; Stockholm. 2010.
12. Rempp KA, Brix G, Wenz F, Becker CR, Guckel F, Lorenz WJ. Quantification of regional cerebral blood flow and volume with dynamic susceptibility contrast-enhanced MR imaging. *Radiology*. 1994; 193(3):637–641. [PubMed: 7972800]
13. Patil V, Johnson G. An Improved Model for Describing the Contrast Bolus in Perfusion MRI. *Med Phys*. 2011; 38(12):6380–6383. [PubMed: 22149821]
14. Bahn MM. A single-step method for estimation of local cerebral blood volume from susceptibility contrast MRI images. *Magn Reson Med*. 1995; 33(3):309–317. [PubMed: 7760699]

15. Zhao JM, Clingman CS, Narvainen MJ, Kauppinen RA, van Zijl PC. Oxygenation and hematocrit dependence of transverse relaxation rates of blood at 3T. *Magn Reson Med*. 2007; 58(3):592–597. [PubMed: 17763354]
16. Bleeker EJ, van Osch MJ, Connelly A, van Buchem MA, Webb AG, Calamante F. New criterion to aid manual and automatic selection of the arterial input function in dynamic susceptibility contrast MRI. *Magn Reson Med*. 2011; 65(2):448–456. [PubMed: 21264935]
17. van Osch MJ, van der Grond J, Bakker CJ. Partial volume effects on arterial input functions: shape and amplitude distortions and their correction. *J Magn Reson Imaging*. 2005; 22(6):704–709. [PubMed: 16261570]
18. Kjolby BF, Mikkelsen IK, Pedersen M, Ostergaard L, Kiselev VG. Analysis of partial volume effects on arterial input functions using gradient echo: a simulation study. *Magn Reson Med*. 2009; 61(6):1300–1309. [PubMed: 19365857]

FIG. 1. Measured (points) and fitted (solid lines) venous signal intensity time curves from five patients at 1.5T (a) and 3T (b). The fitted curves were calculated using the relaxivity parameters that gave the best agreement between the area under the bolus, and steady state amplitude of arterial and venous concentration time curves.

FIG. 2. Arterial (red) and venous (*in vitro* – black; *in vivo* – blue) relaxivity calibration curves at 1.5T (a) and 3T (b). Curve coefficients are given in table 1.

FIG. 3.

Arterial and venous CTCs at 1.5T (a) and 3T (b). The discontinuities in the *in vitro* venous curves are because the same value of ΔR_2^* corresponds to two different concentrations below about 2 mM (see Fig. 2). The curve was therefore obtained by interpolation between zero and the first unambiguous value of ΔR_2^* .

Table 1

Relaxivity coefficients for Eq. [3] (curves shown in fig. 2). Arterial coefficients have been determined by references 4 and 7 for 1.5 and 3T measurements, respectively, and *in vitro* bulk blood coefficients from reference 5.

		q	p	a
Arterial	1.5T	0.74	7.62	0
	3T	2.61	0.5	0
<i>In vivo</i> fitting	1.5T	0.0018	19.0	0.0086
	3T	0.74	12.1	0.0095
<i>In vitro</i> bulk blood	1.5T	6	−11	−0.046
	3T	18	−35	0.037