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T_1 Effects in Sequential Dynamic Susceptibility Contrast Experiments

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Residual effects of an initial bolus of gadolinium contrast agent have been previously demonstrated in sequential dynamic susceptibility contrast MR experiments. While these residual effects quickly reach a saturation steady state, their etiology is uncertain, and they can lead to spurious estimates of hemodynamic parameters in activation experiments. The possible influence of T_1 effects is now investigated with experiments in which T_1 weighting is varied as well as with serial regional T_1 measurements. Little evidence for significant residual T_1 effects is found, suggesting instead that susceptibility effects underlie these observations. An initial saturation dose of contrast agent minimizes this effect. © 1998 Academic Press

Key Words: **fMRI; contrast agents; susceptibility contrast; relaxation time; cerebral blood volume.**

INTRODUCTION

The dynamic susceptibility contrast (DSC) technique is a sensitive and powerful tool for studying cerebral hemodynamics (*1, 2*). However, in order to assess the effect of an activation on relative cerebral blood volume (relCBV) measurements, sequential bolus experiments may be necessary. We previously demonstrated a residual effect in multibolus experiments, observing differences in ΔR_2–time curves between first and subsequent contrast injections. In particular, compared to data obtained with an initial injection, we consistently observed increased peak height and curve width, and a persistent elevation of endline following additional injections (*3*). We also found that these changes reached near steady state upon subsequent bolus injections of contrast agent, and that, if not accounted for, they may lead to spurious estimates of relCBV changes associated with activation (*3*).

The etiology of these residual effects has remained uncertain. Similar effects were previously noted in high-dose-repeated first-pass studies in cats (*4*), and appeared to have a T_1 component, although a persistent susceptibility effect was also demonstrated. Our initial experiments were performed using a spin-echo echo-planar-imaging (EPI) sequence (TR = 1 s, TE = 100 ms) which allowed for both high temporal resolution and small vessel selectivity for CBV imaging (*5, 6*). However, as this sequence has both T_1 and T_2 weighing, distinguishing a residual susceptibility effect from a T_1 effect is difficult. Yet, determining the etiology of such effects has important implications for activation studies utilizing sequential DSC experiments. Not only does this lead to a better understanding of the DSC experiment, but it aids in determining the best strategy for reducing the influence of these residual effects, be it using a presaturation dose or a data correction method after the fact.

In order to investigate the influence of T_1 effects on these data, we have conducted a series of spin-echo EPI multibolus DSC experiments under conditions with different T_1 weighting, by varying the flip angle (θ) and the repetition time (TR). T_1 effects are proportional to the degree of T_1 weighting; therefore, reducing T_1 weighting should reduce these effects in the resulting images which are spin density and T_2 weighted. In addition, we have mapped brain T_1 values under the original experimental conditions in order to directly assess possible T_1 changes associated with repeated boluses of gadolinium contrast agent.

MATERIALS AND METHODS

Studies were performed on nine normal healthy men (age range 20–34 yr old) using a 1.5-*T* scanner modified for single-shot EPI studies (Instascan, ANMR Inc.). All subjects were scanned in the resting state with eyes open. Spin-echo EPI images (TR = 1 or 2 s, TE = 100 ms, 3 × 3 mm resolution) were acquired in the axial plane in 7-mm slices during each TR interval for 100 s. Twenty seconds into acquisition, 0.075 mmol/kg gadoteridol (GD; ProHance, Bracco Diagnostics, Inc., Princeton, NJ) was administered by rapid intravenous bolus injection (3–5 s). Subjects received four GD contrast boluses, each injection separated by 10 min. Studies were performed at varying flip angles (θ = 45°, 30°, and 15°); in addition, two studies were performed at TR = 2 s (one at θ = 90°, one at θ = 45°).

For data analysis, one axial slice, located immediately rostral to the level of the lateral ventricles, was selected for each study. Mean whole-slice brain MR intensity was measured for each shot, and transformed according to the relationship (*2*)

$$\Delta R_2 = -\ln[S_t/S_0]/\mathrm{TE}, \qquad [1]$$

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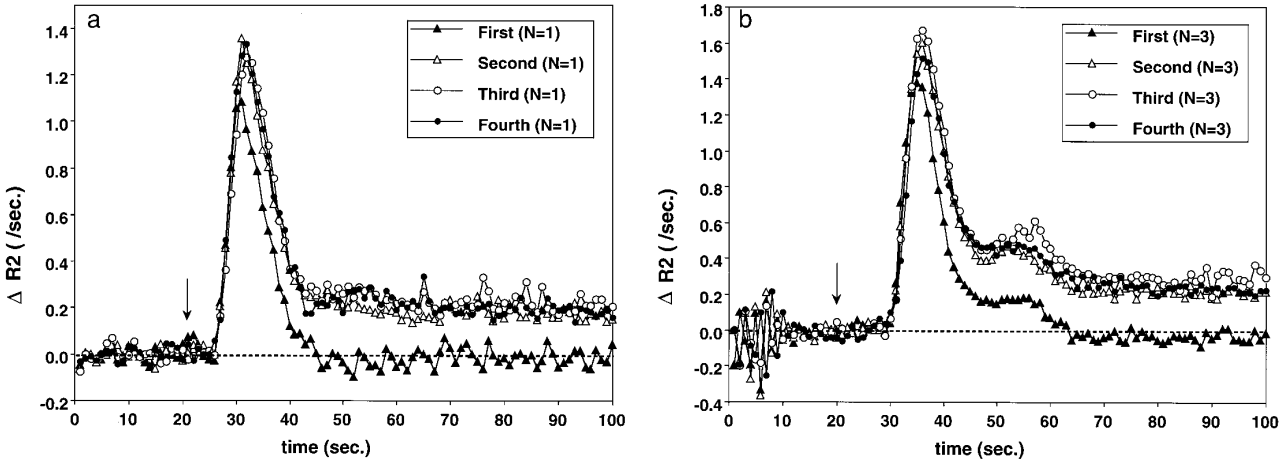

FIG. 1. (a) ΔR_2–time curves for a 4-bolus study in a single subject with TR = 1 s, and $\theta = 90°$ (SF = 32.9%) showing residual effect and steady state with subsequent runs. Contrast injection denoted by arrow. (b) Averaged ΔR_2–time curves for 4-bolus studies in three subjects with TR = 1 s, and $\theta = 30°$ (SF = 6.2%) showing persistence of residual effect and steady state with subsequent runs. Contrast injection denoted by arrow.

where S_0 is precontrast baseline signal intensity and S_t is signal intensity at any time t. RelCBV was calculated by numerical integration of first pass ΔR_2–time curve data (*2, 3*). Endline was determined by averaging the final 20 s of ΔR_2 data for each DSC run.

The degree of T_1 weighting of the images is represented by the saturation factor (SF), which is the percent change of the steady state value of the *z* component of the magnetization (M_z) relative to the fully relaxed value (M_0):

$$\mathrm{SF} = 100(M_0 - M_z)/M_0. \qquad [2]$$

A SF of 100% indicates complete saturation of the longitudinal magnetization; conversely, a SF of 0% describes a fully relaxed sequence with no T_1 weighting. For a long series of θ pulses separated by TR, M_z immediately preceding a pulse may be expressed according to the following relation, which considers only the longitudinal magnetization and does not include effects from coherence refocusing phenomena such as stimulated echoes (*7*):

$$M_z = M_0 \frac{1 - \exp(-\mathrm{TR}/T_1)}{1 - \cos(\theta)\exp(-\mathrm{TR}/T_1)}. \qquad [3]$$

In our experiments the calculated SF ranged from a maximum of 32.9% for TR = 1 s and $\theta = 90°$ to SF = 1.6% for TR = 1 s and $\theta = 15°$, assuming a tissue T_1 of 900 ms (*8*).

In addition to varying the T_1 weighting of our sequences, we mapped T_1 values in three subjects before and 10 min after the injection of a dose of 0.075 mmol/kg gadoteridol. To accomplish this, we performed inversion time (TI) stepping, using an inversion recovery EPI sequence (TR = 20 s, TE = 41 ms, initial TI = 200 ms, 16 step increments in TI of 100 ms each, matrix = 128 × 64, FOV = 40 × 20 cm). T_1 maps were derived from these data on a pixel by pixel basis and were analyzed by regions of interest (ROI) in the frontal gray matter, parietal white matter, and the whole slice used in the DSC analysis.

Finally, in order to assess the effect of scanner stability as well as the effect of our baseline normalization procedures on these findings, we studied a single subject continuously for 15 min (single 7-mm slice, SE EPI; TR = 1 s, TE = 100 ms, $\theta = 90°$) with two 0.1 mmol/kg gadoteridol bolus injections separated by a 10-min interval.

RESULTS

We observed a residual effect of the initial bolus of contrast agent on subsequent bolus ΔR_2–time curves in each of the nine experiments with reduced T_1 weighting. These effects were similar to those we had observed in our earlier studies performed at intermediate T_1 weighting (SF = 32.9%) (for example, see Fig. 1a). Figure 1b illustrates these findings in three subjects studied at a SF of 6.2%, showing a dramatic change in the curve profile following the first bolus of gadoteridol, but little change following subsequent doses. There was also little effect of T_1 weighting on the relCBV calculated from these data. As illustrated in Table 1, the apparent increase in relCBV from first to second DSC run remains constant despite substantial variation in SF over more than an order of magnitude.

The relationship between SF and change in relCBV from first to second bolus was evaluated by linear regression analysis. We found no relationship between SF and ΔCBV (slope = 0.27, $R^2 = 0.009$, $p = 0.8$). The *y* intercept, representing the predicted ΔCBV with no T_1 weighting, was 23% (95% confidence interval 6–40%, $p = 0.02$). The statistical analysis of ΔCBV at each SF, as shown in Table 1, was

TABLE 1

The Calculated Apparent Increase in relCBV at the Second DSC Run, Elevation in Endline at the Second DSC Run, and the Estimated Saturation Factor for Each Experimental Condition (±1 SD)

TR (s)	θ (°)	Saturation factor (%)	Increase in relCBV (%)	Elevation in endline (s^{-1})	N	P^a
1	90	32.9	27.7 ± 17.6	0.12 ± 0.08	30	<0.0001
1	45	12.6	32.4	0.29	1	N/A
2	90	10.8	18.3	0.11	1	N/A
1	30	6.2	25.5 ± 13	0.22 ± 0.01	3	0.01
2	45	3.4	21.7 ± 16.5	0.28 ± 0.03	2	0.04
1	15	1.6	25.2 ± 14.9	0.12 ± 0.07	2	0.12

Note. Summary results are from original experiments. (TR = 1 s, θ = 90°) is shown for comparison (*3*).

[a] One-tailed paired *t* test comparing relCBV at first and second DSC injections.

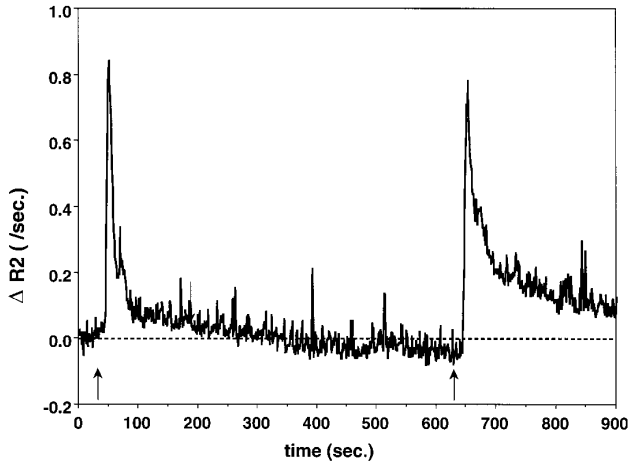

FIG. 2. ΔR_2–time curve from one subject scanned continuously for 15 min (TR = 1 s, θ = 90°), with two contrast bolus injections separated by a 10-min interval (arrows). Note initial return to baseline but subsequent marked elevation.

limited in part by the small number of observations. However, considering the entire group as a whole, with a mean SF of 5.8%, the increase in relCBV from first to second injection was 24.5% (p = 0.00007, paired *t* test, one-tailed).

The T_1 mapping data, before and after the administration of contrast, showed only a 2–3% decrease in T_1 in each region sampled (whole slice, gray matter, and white matter) (Table 2).

Results from the single-slice continuous acquisition with two bolus injections of contrast separated by a 10-min interval show that the endline following the first injection returns fairly quickly to baseline, while it is markedly elevated following the second injection (Fig. 2). These results confirm scanner stability throughout the experiment as well as the equivalence of first and second baselines.

DISCUSSION

In a series of experiments designed to evaluate the influence of T_1 on the residual effect previously seen in multibolus DSC experiments, we found a persistent effect despite significantly reducing experimental T_1 weighting. In these experiments, the T_1 weighting, as determined by the SF (7), was reduced by more than an order of magnitude. Although comparison of the degree of residual effect is difficult given the limited number of studies at each SF, there does not appear to be any relationship between our measures of residual effect (such as the apparent increase in relCBV between first and second DSC runs, and the elevation of endline above baseline) and T_1 weighting. In fact, our predicted increase in relCBV with no T_1 weighting (23%, 95% confidence interval 6–40%) agrees well with our initial finding of a 27.7% increase in 30 subjects studied at a moderate T_1 weighting (*3*).

In addition, in the experiments with the lowest T_1 weighting, explanation of the observed ΔR_2–time curve endline elevations based exclusively on T_1 effects would require that the contrast bolus alters T_1 in our ROI by ~30%. It is unlikely that tissue T_1 undergoes this degree of shortening; in fact, our T_1 mapping data suggest that the shortening is <4%. Such small changes in tissue T_1 do not appear to be enough to account for the large signal changes that we have observed. Blood T_1 may well remain persistently and significantly shortened, and we may well initially observe small T_1 effects (see below). However, given the small percentage of our whole brain ROI occupied by blood vessels (<5%, (*9*)), it is unlikely that changes in blood T_1 underlie these findings. Therefore, while we cannot exclude some degree of persistent T_1 effect as the basis for the residual susceptibility effects seen in multibolus DSC experiments, these data suggest that they do not play a predominant role.

In order to explain our findings, it is important to review the changes that we have observed in the ΔR_2 curves. With the initial contrast injection, ΔR_2 values return to a value slightly below baseline, corresponding to a slight increase in

TABLE 2

Results from T_1 Mapping in Three Subjects Before and 10 min after Bolus Injection of 0.075 mmol/kg Gadoteridol

Region	T_1 (ms) before Gd	T_1 (ms) after Gd	Change (%)	Average ROI area (cm^2)
Whole slice	1106 ± 35	1078 ± 42	−2.5	182
White matter	709 ± 34	686 ± 22	−3.2	2.93
Gray matter	1223 ± 20	1188 ± 44	−2.9	4.30

Note. Studies performed at SF = 32.9%. Mean ± SD from two separate measurements.

signal intensity, consistent with a small T_1 effect, even with our initial weighting (see Fig. 1a and Fig. 2). Subsequently, however, there is residual elevation of ΔR_2 values following sequential bolus contrast injections, corresponding to a net decrease in actual signal intensity below precontrast baseline. Therefore, significant persistent susceptibility effects beyond the first pass of contrast agent remains the most likely explanation for these data. Such effects seem to dominate any further T_1 effects, if present. In addition, besides lack of direct evidence for significant T_1 effects, pharmacokinetic evidence favors residual susceptibility effects. We previously observed that these residual effects persist at for least 2 h but resolve within 4 h following an initial dose of contrast, a time period that closely parallels the elimination half-life of gadoteridol (1.57 h) (*3, 10*). However, the precise etiology of the residual susceptibility effects, such as possible transient intravascular pooling or endothelial adherence, nonlinearity of contrast concentration, and ΔR_2, remains unclear. An alternative hypothesis, a direct effect of bolus injection of MR contrast agents on cerebral hemodynamics, seems particularly unlikely in light of recent evidence showing lack of any such effect in rats receiving doses of gadopentetate dimeglumine compared to those used in our study (*11*).

The most important implication of residual susceptibility effects is their impairment of sequential CBV measurements. Recognition of these effects are critical in that they partially violate the inert intravascular tracer requirement of tracer kinetic theory upon which analysis of first-pass experiments is based. However, a presaturation dose of contrast agent prior to a baseline measurement, as we have previously demonstrated, provides an acceptable solution to the problem of these residual effects interfering with repeated CBV measurements in activation studies. The alternative solution of attempting to correct DSC data after the fact is less attractive in view of the lack of significant T_1 effects.

In summary, residual contrast agent effects were seen over a wide range of T_1 weighting, and do not appear to be attenuated in experiments with a minimal degree of T_1 weighting. This implies that these effects are not primarily T_1-related, but rather reflect persistent susceptibility effects. Accounting for such effects is important when performing sequential bolus DSC experiments, which extend the utility of this technique for finding changes in relative CBV associated with activation.

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