Perfusion Imaging with NMR Contrast Agents*

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Knowledge of regional hemodynamics has widespread application for both physiological research and clinical assessment. Here we review the use of MR contrast agents to measure tissue perfusion. Two primary mechanisms of image contrast are discussed: relaxivity and susceptibility effects. Relaxivity effects result from dipolar enhancement of T1 and T2 rates. Because tissue T1 rates are intrinsically smaller, the dominant effect is shortening of T1 relaxation times. The second mechanism of image contrast is the variation in tissue magnetic field produced by heterogeneous distribution of high magnetic susceptibility agents. Quantitation of tissue perfusion requires a detailed understanding of the relation between contrast agent concentration and associated MR signal changes. Studies to date show a linear relationship between contrast agent concentration and rate change in most organs. The exact nature of this relationship in the dynamic setting of rapid contrast agent passage through the microcirculatory bed is less well established. If this relationship is known, tracer kinetic modeling can be used to calculate regional blood flow and blood volume. Data are presented which indicate that this approach is feasible, and suggest the potential of contrast-enhanced NMR for high resolution in vivo mapping of both physiology and anatomy. © 1990 Academic Press, Inc.

INTRODUCTION

In the years since the first magnetic resonance images were produced by Lauterbur (1) it has become evident that conventional T1- and T2-weighted images and relaxation time measurements do not, of themselves, provide a particularly specific means of characterizing diseased tissue, and that they can lack sensitivity in certain circumstances (2). Of particular concern is the inability of conventional MR imaging to detect signal changes in areas of acute ischemia. Because vascular disease of the brain and heart, with the associated tissue ischemia, is a major health problem responsible for over half the deaths in the country annually, MR techniques that accurately measure normal and abnormal tissue perfusion may have significant impact in the diagnosis and management of patients with ischemic disease of the these and other organs.

Although one of the great advantages of MR imaging is the high degree of intrinsic tissue contrast present from tissue relaxation times, chemical shifts, and bulk flow, the use of intrinsic contrast mechanisms to image tissue microcirculation remains

challenging for several reasons. Most important of these are the very slow flow rates within capillaries (about 0.5–1.5 mm/s), as well as the small volume fractions of the intravascular bed in most tissues (2–10%) (3). For these reasons there has recently been increased interest in the use of NMR contrast agents to enhance sensitivity to tissue microcirculatory changes, with the goal of direct quantitative measurement of blood flow and volume.

Contrast agents have been used in nearly all forms of radiographic procedures. The means by which MR contrast agents affect image contrast is unique to the NMR experiment. The interactions between some MR contrast agents, notably paramagnetic chelates, and tissues have been studied extensively (4–6). The mechanism of action for these compounds is dipolar interaction between proton nuclear spins and unpaired electrons within the compounds, and in most tissues they have their dominant effect on the longitudinal relaxation times T1. As a result, image contrast is most apparent on T1-weighted spin and gradient echo images. With these compounds the physical interaction of the paramagnetic’s unpaired spin and the surrounding aqueous environment has been studied in detail (7).

Other mechanisms of signal contrast have also been studied. Recent work has demonstrated that high magnetic susceptibility agents, including paramagnetic lanthanide chelates and superparamagnetic iron oxides, can affect T2-weighted spin and gradient echo images as profoundly as classical dipolar relaxation can affect T1 images (8). The mechanism of image contrast here depends on the compartmentalization of the agent, rather than direct interaction of tissue water with the unpaired spins.

Both of the contrast mechanisms discussed above have been used with agents designed to enhance the sensitivity of conventional MR images to the presence of neoplastic and other diseases. The use of contrast agents to measure tissue perfusion also has precedent. For example, the use of radiolabeled compounds to study tissue perfusion motivated the development of tracer kinetic models. To apply the formalism of tracer kinetics to MR measurement of tissue blood flow and volume, an understanding of the contrast mechanisms discussed above is required to determine the relationship between image signal change and local contrast agent concentration. In particular, the kinetics and compartmentalization of contrast agent delivery to tissue, as well as how these affect MR image intensity, must be well characterized. With this relation in hand it should be possible to generate MR concentration–time curves. Analysis of these data using appropriate kinetic modeling will then allow for the determination of tissue microcirculatory parameters. Such models have been applied to a wide range of quantitative cross-sectional imaging studies, particularly with positron emission tomography (PET) (9–11) and contrast CT (12–15).

This report reviews current concepts in the use of MR contrast agents to measure parameters related to tissue perfusion. The two primary mechanisms of image contrast—relaxivity and susceptibility effects—will be presented, along with the analysis required to convert MR image data into concentration–time data. Finally, we briefly review how concentration–time data can be used to calculate regional blood flow and volume.

RELAXIVITY CONTRAST AGENTS

The relationship between aqueous paramagnetic lanthanides and proton relaxation enhancement has been known since Bloch’s earliest NMR experiments (16),
with a detailed model for such interactions evolving from the work of Solomon (17) and Bloembergen (18). A current review of this phenomenon is presented by Lauffer (6), emphasizing that the dominant mechanism for relaxation enhancement is the dipole–dipole interaction between the large free electron spins of the paramagnetic ion and the proton spins. An extensive literature has developed on the tissue relaxation enhancement of lanthanide chelates (19-23). This class of agents includes the familiar Gd(DTPA)$^{2-}$, the only agent as yet approved for routine human use in the United States.

Despite some complexities of extending earlier work to tissues in vivo, certain basic characteristics seem evident. First, relaxation enhancement decreases both T1 and T2 relaxation times. However, because T1 rates (1/T1) are intrinsically smaller than T2 rates (1/T2) in most tissues, relaxation time changes on a percentage basis are much greater for T1 than T2. For this reason, compounds whose main mechanism of action is dipole–dipole relaxation enhancement are often thought of as “T1 agents.” The second feature of relaxivity contrast is the relationship between the agent’s concentration and the degree of relaxation enhancement. The correlation between observed NMR signal change and contrast concentration is the key link in applying compartmental models to measure microcirculation. In most studies to date, an essentially linear relationship between tissue lanthanide chelate concentration and T1 rate change has been observed (24, 25), including studies of the blood (26) and myocardium (27). For a given tissue [i], such a relationship takes the form

$$\Delta(1/T1_{\text{bulk}}) = \Delta R1_{\text{bulk}} = k_1 [\text{Tissue}],$$  

where $\Delta(1/T1_{\text{bulk}}) = \Delta R1_{\text{bulk}}$ is the difference between tissue T1 rates with and without contrast enhancement, $k_1$ is a tissue and field strength specific constant, and [Tissue] is the tissue concentration of the agent.

To produce monoexponential longitudinal relaxation rate enhancement of this kind assumes that all tissue water molecules have direct and ready access to the coordination sites of the paramagnetic ion in time frames that are short compared to the observed relaxation times. In this “fast exchange” model, the bulk or average tissue relaxation rate changes can be calculated from the compartmental relaxation times,

$$1/T1 = \sum v_i/T1_i,$$  

where $v_i$ represents the fractional volumes of distinct tissue compartments (e.g., intravascular, interstitial, and intracellular) and $T1_i$ the relaxation times within each of the $i$ compartments.

The assumptions of this model depend on both the compartmentalization of the agent within the tissue and the exchange rates of water across these compartments. For example, in the brain, where the blood–brain barrier prevents diffusion of paramagnetic chelates out of the intravascular space and limits water exchange across the vascular endothelium, only small T1 effects are normally seen (8). Within the brain then, the assumptions behind the fast exchange model may not hold true, and slow or intermediate exchange models may more accurately reflect the dynamics of tissue relaxation enhancement in the presence of an intact blood–brain barrier. In fact, relaxation agents have been proposed as a means to measure capillary water permeability by assessment of water exchange times (28, 29).
In most other organs, however, empirical data suggest that tissue longitudinal relaxation rate changes are proportional to tissue contrast agent concentration. Unfortunately, an important limitation of these data is that most were obtained under steady-state or equilibrium conditions. For extracellular tracers such as Gd(DTPA)$^{2-}$, this means that the agents had nearly equal intravascular and interstitial concentrations when the relaxation times were measured. In dynamic studies (needed for measurement of tissue blood flow) this will not, in general, be the case (as extraction fractions may be less than 1). Whether water exchange times are rapid enough between compartments to validate fast exchange relaxation kinetics will await determination of relaxation times in dynamic settings. Establishing in different organs the nature of the specific relationship between compartmental concentrations of contrast agents and NMR-observable parameters such as tissue T1 rate changes is a fundamental step toward applying paramagnetic proton relaxation enhancement to measure tissue perfusion.

SUSCEPTIBILITY CONTRAST AGENTS

Variations in tissue magnetic susceptibility can profoundly affect MR images. As with relaxivity contrast, understanding the mechanism by which microscopic regions of heterogeneous magnetic susceptibility affect MR signal intensity is essential to understanding the relationship between contrast agent concentration and MR signal intensity.

Magnetic susceptibility is the proportionality constant between an applied magnetic field and the resultant magnetization established within the material. For example, the unpaired electrons of elements such as iron, gadolinium, and dysprosium have electron magnetic dipoles that respond to an externally applied magnetic field in much the same way as the weaker nuclear magnetic dipoles, tending to align themselves with the applied field. As with nuclear spins, only a fraction of the electron spins will ordinarily contribute to this induced net magnetization. If the unpaired spins are present in sufficient concentration this effect will dominate the weaker (paired electron) diamagnetic properties, and the induced magnetization will be aligned with, and not opposed to, the applied field (positive magnetic susceptibility). Such materials are termed paramagnetic (30, 31). If a large number of such unpaired spins are contained within crystal structures (called domains) such that their magnetic moments couple synergistically, then an even greater number of dipoles will align themselves with the applied field. These materials are labeled superparamagnetic or ferromagnetic, depending on the size and precise nature of the crystal domains (32-34).

If homogeneously distributed, aqueous materials with high magnetic susceptibility (e.g., solutions with significant concentrations of paramagnetic ions) will display relaxation properties governed by the relaxivity constants discussed above. This results in increased signal intensity on MR images designed to be sensitive to T1 relaxation differences. If heterogeneous in distribution, however, regions of high and low magnetic susceptibility within voxels of an image can have a pronounced effect on MR images not predicted by classical Solomon–Bloembergen relaxivity enhancement, leading to significant signal losses. These effects can be understood by remembering that magnetic susceptibility differences affect the local resonance frequency by modi-
fying the magnetic field experienced by nearby water protons. This can affect MR images in three ways. First, by increasing the diversity of magnetic fields within a voxel, variations in magnetic susceptibility lead to an increase in water resonance linewidth. This results in decreased signal from pulse sequences which do not fully refocus static inhomogeneities, such as gradient echoes or spin echoes with temporal offsets in their 180° pulses (35). The decreased signal seen on gradient echo or offset spin echo sequences in these circumstances is commonly labeled susceptibility induced T2\* shortening (35). Second, in these same pulse sequences, the variations in magnetic field can lead to a net displacement in the resonance frequency throughout a whole voxel. This in turn results in phase shifts seen with phase sensitive imaging techniques, such as phase mapping or “zebra” techniques (36,37). In both cases the effect (signal loss or phase shift) increases with greater echo times or 180° offset times.

Third, in pulse sequences with complete refocusing of static inhomogeneities (e.g., spin echoes), increases in resonance linewidth or shift in resonance frequency will not directly lead to signal loss or phase distortions. However, if the echo time is sufficient to allow substantial diffusion of water through areas of different magnetic field during the TE period, then the magnetic field variations become essentially a dynamic phenomenon in the reference frame of the spin. Under these conditions the requirement for spin echo rephasing—the presence of only static inhomogeneities—is violated. This leads to dephasing and hence to signal loss on spin echo images as well. Although this effect can be less pronounced than on gradient echo images, with sufficient TE the signal attenuation can be quite significant. This is often labeled a T2 effect; however, it must be differentiated from what we more typically think of as T2 decay in that it is recoverable with multiecho experiments such as a short TE CPMG sequence (as are other diffusion-related phenomena), while true T2 signal attenuation is not.

These effects provide the opportunity for introducing exogenous contrast agents that can be designed to alter the magnetic susceptibility of the tissue in a predictable way (8). An example is the intravenous administration of paramagnetic chelates, such as Gd(DTPA)\(^2\) or Dy(DTPA)\(^3\). Because of their large magnetic moments, these agents transiently alter the magnetic susceptibility of tissues during passage through the microvascular bed, with resultant changes in T2 and T2*.

Figure 1 shows data obtained from such an experiment in the dog brain (38,39), using a 2.0-T high-speed imaging system developed by Advanced NMR Systems Inc. (40,41). Although the vascular space is a small fraction (>4%) of total tissue volume, the compartmentalization of contrast agent within the intravascular space leads to a >50% transient drop in signal following administration of Dy(DTPA)\(^2\). This reflects local field inhomogeneities that extend beyond the vascular space, affecting much of the surrounding brain tissue. This effect can be seen on both rapid spin echo and gradient echo imaging using conventional as well as “single-shot” imaging techniques. Rapid imaging techniques are especially suited for studying this phenomenon due to the high temporal resolution needed to characterize the passage of these agents through the vascular space (39,42).

Several theoretical models have been proposed to account for this observed behavior (43–46). Although their details are beyond the scope of this review, they can be broken into three categories. The first class assumes rapid movement of the water...
FIG. 1. (A) Sequential coronal sections through a canine head before (left) and after (right) bolus contrast injection (0.2 mmol/kg Dy(DTPA)) show the regional distribution of dynamic changes in brain signal intensity due to cerebral transit of contrast agent. Signal intensity from a phantom below the animal's head remains constant. Each instant scan gradient echo image (128 X 64, TE = 14 ms) was acquired in 25 ms (TR = 1000 ms). Significant differences in signal attenuation and kinetics are observed for gray and white matter regions. (B) Changes in dog brain signal intensity were measured in cortical gray (■, △) and periventricular white matter regions (□, ▽). The figure shows two separate contrast injections under the same conditions in the same animal, demonstrating the reproducibility of the experiment.

spins across the regions of heterogeneous field (43), and as such can be considered a fast exchange model, analogous to those developed in relaxation theory. This leads to analytic expressions for measured T2 relaxation rates. The assumptions of this model are likely to be met in cases where the size of the high susceptibility regions is small (such as ferritin deposits within a hemorrhage), or where water diffusion rates are high.

The second class of models can be considered the opposite extreme, where the water spins can only be assumed to sample a small region of the heterogeneous magnetic field distribution during the echo time. In this "slow exchange" case, the mag-
Fig. 2. Relationship between brain tissue T2 relaxation rate and contrast agent concentration. Peak change in $\Delta R2$ versus contrast-induced susceptibility change is shown. Susceptibility change is in arbitrary units proportional to concentration and to the square of the magnetic moment of the contrast agent.

Magnetic field experienced by the spins can be thought of as approaching a linear field gradient. By modeling the distribution of such linear gradients through space, expressions for the behavior of the transverse magnetization can be derived (44). The conditions of this model are likely to be satisfied in cases where the regions of heterogeneous magnetic field are large, or the diffusion coefficient of water is small.

In the case where water exchange is neither obviously fast nor slow (the so-called “intermediate exchange” regime), simplified analytic expressions for relaxation behavior become difficult to derive. For this reason, the third class of models uses Monte Carlo techniques to explicitly follow spins through heterogeneous field distributions. In simplest form these techniques have been applied to predict the distribution of field strengths, and hence static lineshapes, within tissues (45). In more challenging applications, these techniques have modeled not only static but dynamic (diffusion-related) spin dephasing (46, 47).

Recent work seems to indicate that this intermediate exchange regime may in fact be relevant to the perfusion problem. Preliminary data appear to show that the results of this modeling may differ significantly from those predicted from either fast or slow exchange calculations (47). One question of particular relevance is the predicted relationship between the measured T2 relaxation rate enhancement and the concentration of high susceptibility materials within the sample. Both empirical data (8, 48) (see Fig. 2) and preliminary Monte Carlo modeling (44, 47) show a linear relationship between tissue contrast agent concentration and T2 rate change ($\Delta(1/T2^*) = \Delta R2$), i.e.,

$$\Delta R2 = k_2 \text{ [Tissue]},$$  \[3\]

where $k_2$ is a tissue, field strength, and pulse sequence specific constant. This is analogous to that seen in Eq. [1] for relaxivity agents. Assuming monoexponential behavior, signal intensity changes following contrast agent injection can be related to the T2 rate change by the expression
Combining Eqs. [3] and [4], signal intensity changes can be converted to a tissue concentration–time curve

\[ S(t) = S_0 e^{-\frac{TE}{R(t)}}. \]  \[4\]

where \(S(t)\) is the tissue signal with contrast agent present at time \(t\), and \(TE\) is the echo time. The validity of the above relationship in normal and pathologic states in several organs is still being elucidated, and remains a key question in attempts to use MR contrast agents for measurement of tissue perfusion.

**MEASUREMENT OF TISSUE PERFUSION**

Given concentration–time curves produced from either relaxivity- or susceptibility-based contrast, an extensive literature exists to guide us in utilizing this information to derive regional blood flow and blood volume. Although it is beyond the scope of this review to discuss this topic in detail, an outline for how such techniques can be applied to NMR image data is presented, along with preliminary data suggesting the feasibility of such an approach.

A guiding principle for the analysis of concentration–time data was outlined almost a century ago by Stewart (49) and is known as the Central Volume Theorem. Derived simply from mass conservation, this theorem states that tissue blood flow \(F\) can be determined by the ratio

\[ F = \frac{V}{MTT}, \]  \[6\]

where \(V\) is the volume of distribution of the agent within the tissue (e.g., the tissue blood volume for an intravascular agent), and the mean transit time (MTT) is the average time it takes any given particle of contrast agent to pass through the tissue.

There are several reasons why this seemingly simple equation may in practice be difficult to solve. First, the volume of distribution of the agent may, as discussed previously, be biologically multicompartmental, with transfer of the agent between different tissue volumes occurring at different rates. To account for this, the details of the passage of the agent through the tissue must be modeled, and several basic approaches to this sort of modeling have been proposed for different classes of agents (50, 51). Second, even for single-compartment agents such as purely intravascular markers, measurement of the MTT can be difficult. This is because the definition of MTT involves the transit of an idealized bolus from an instantaneous delta function injection. The tissue concentration–time curve response to such a bolus is called the tissue residue function, and for obvious reasons cannot usually be measured in vivo.

The actual measured tissue concentration–time curve, \(\text{Tissue}(t)\), is by superposition the convolution of the arterial input function \(\text{Art}(t)\) and the residue function \(\text{RF}(t)\):

\[ \text{Tissue}(t) = \text{Art}(t) \ast \text{RF}(t). \]  \[7\]

To measure the residue function \(\text{RF}(t)\), and the associated MTT, we need to deconvolve the measured tissue concentration–time curve with the observed arterial blood input function. \(\text{Art}(t)\) can be measured directly with arterial blood sampling,
Fig. 3. Cerebral blood volume versus arterial pCO\(_2\). Numerical integration of the area of the concentration–time curve obtained during different levels of pCO\(_2\), for a white matter region. The expected change in blood volume with increasing pCO\(_2\) is readily observed.

as is conventionally done with PET imaging, or could in principle be accomplished directly from MR images if sufficient temporal and contrast resolution is present. Tissue(t) could (subject to the limitations discussed above) be determined regionally or on a voxel by voxel basis from our imaging experiments. However, the measured Tissue(t) curves can include contributions due to tracer recirculation which must be eliminated prior to deconvolution, in order to extract volume and flow information. This can be accomplished by exponential extrapolation, numerical integration, or fitting to a gamma-variate function with a recirculation cutoff (52–54)

\[
\text{Tissue}(t) = Q(t')e^{-(t/b)},
\]

where \(Q\), \(r\), and \(b\) are constants. A variety of functional parameters can then be analytically calculated, including the area under the concentration–time curve which is proportional to local blood volume (14, 55, 56). The accuracy with which the MTT can be determined will depend on the quality of both the Art(t) and the Tissue(t) data. In the case of freely diffusible markers this is made somewhat simpler by the slower transit times through the tissues; thus the measurement of MTT is less dependent on the arterial input curve. For purely intravascular markers the transit is so rapid that a well-characterized bolus is needed to obtain accurate measurement of MTT (42).

In addition to measurement of MTT, determination of blood flow requires knowledge of the volume of distribution of the agent. For intravascular agents this is the tissue blood volume, an important physiological parameter itself. Measurement of blood volume \(V\) can be made by integrating the tissue concentration–time curve and normalizing to the integrated arterial (input) data (14, 42, 51, 55), i.e.,

\[
V = \frac{\int \text{Tissue}(t)}{\int \text{Art}(t)}.
\]

This has several important consequences. First, because the blood volume deter-
FIG. 4. “Single-shot” transverse images in a patient status post chronic MCA infarct, depicting regional variations in signal intensity before (A) and 20 s after (B) IV bolus administration of 0.1 mmol/kg Gd(DTPA)$_2$$. (C) Functional NMR image of the brain. Image intensity is proportional to regional blood volume, calculated on a voxel by voxel basis by integration of the concentration–time data. Known resting blood volume differences between gray and white matter are well illustrated, as is the region of vascular insult. For comparison, a relative CBV image of a normal volunteer is shown in (D).

mination is reflected in the time-integrated tissue and blood concentration data, measurement of blood volume alone has somewhat diminished need for very high temporal resolution measurements. In measurement of arterial blood data this can mean that samples collected over time do not need to be fractionally measured, and can simply be pooled for an average determination. Second, because the arterial input to an organ is ultimately derived from a common source, measurement of relative blood volume can be made without any knowledge of the arterial concentration–time data. For these reasons attempts to quantify microcirculatory parameters from NMR data have to date focused on the somewhat simpler measurement of blood volume,
as a necessary and important first step toward complete characterization of tissue perfusion.

Two examples of this approach have recently been presented, using both relaxivity and susceptibility contrast. Using albumin-(Gd-DTPA), Moseley and co-workers have measured cerebral blood volume in rodents by measuring T1 relaxation rate changes from NMR images (57). Since the albumin form of Gd(DTPA)$^{2-}$ remains at nearly constant concentration for extended periods within the intravascular space, determination of concentration using bolus injections can be replaced by measurement of equilibrium concentration in both tissue and arterial systems (58, 59). These data are particularly exciting in that image data were used not only to measure tissue agent concentration but also, from images through large vessels, the vascular concentration. These results show that equilibrium relaxivity changes from an intravascular agent can be used to determine absolute tissue blood volume, and their results are in good agreement with other literature values.
Work in our own laboratory has extended these concepts to the measurement of regional relative blood volume from bolus injections using susceptibility contrast (8, 60, 61). Using image data obtained with the use of real-time imaging techniques, Belliveau et al. (38, 39, 48, 62) have obtained high temporal resolution NMR images of the dog brain following injection of Dy(DTPA)²⁻ (see Fig. 1). Using an empirically determined relationship between T2 rate change and tissue dysprosium concentration (analogous to that shown in Fig. 2), estimations of the tissue concentration-time curve were obtained in both gray and white matter regions during hypo-, normo-, and hypercapnic conditions. Because the relationships between blood volumes in gray and white matter and during hypercapnic stress have been well documented using other modalities (63–66), these data have been used to validate the basic assumptions of the susceptibility contrast model, and determine the feasibility

![Image](image-url)
of using bolus concentration–time data to determine parameters of physiologic significance.

The results of this analysis are shown in Fig. 3. From these data, relative tissue blood volumes for gray and white matter as a function of $p$CO$_2$ were calculated and shown to compare favorably with literature values (39, 48, 62). Our data show a linear change in NMR signal over the range of CO$_2$ investigated, in agreement with other methods of measuring CBV (63–66). Although the constant relating observed changes in $\Delta R_2$ to tissue concentration was not determined, if one solves the reactivity equation for two different values of $p$CO$_2$, the ratio of these numbers is dimensionless and can be compared to that observed by other accepted methods. Particularly, the ratio of cerebral blood volume at 80 Torr versus 40 Torr is 1.4 as measured by emission tomography (63, 67). Solving our reactivity equation such as shown in
Fig. 3 at these points yields an average ratio of 1.3 to 1.5. Additionally, by multiple techniques, the measured ratio of the resting cerebral blood volume in gray versus white matter is approximately 2:1 (63, 67–72). Our measurement of the area under the concentration–time curve for cortical gray versus periventricular white matter yielded a ratio of 2.0 ± 0.5.

The advent of whole-body single-shot imaging capability, coupled with the approval of paramagnetic contrast agents for human use, has recently enabled us to demonstrate susceptibility contrast in the human brain, allowing for generation of functional images (48, 73, 74). Using a 1.5-T imaging system developed by Advanced NMR Systems Inc. (Woburn, MA), Instascan gradient echo images (TR = 1000 ms, TE = 60 ms) were acquired in 75 ms. Sequential images at multiple slices were sampled every second following bolus administration of 0.1 mmol/kg Gd(DTPA)²⁻. A transient (∼10 s) signal loss was seen throughout the normal brain after injection, with gray matter signal attenuation of ∼60% (see Figs. 4A and 4B). Using the kinetic modeling discussed previously, functional images depicting relative regional variation in CBV were generated (Fig. 4C). In this patient status post remote MCA infarction, calculated blood volume was significantly reduced in the region corresponding to the known infarct. For comparison, the CBV image of a normal human volunteer is shown in Fig. 4D. Gray/white matter ratios of ∼2/1 were observed, congruent with literature values. The superior spatial (1.5 × 3.0 mm) and temporal (<1 s) resolution of this functional NMR imaging technique promises to provide rapid and safe evaluation of tissue hemodynamics in normal and disease states.

The measurement of relative blood volume involves the integral of the tissue concentration–time curve. However, to calculate blood flow, additional data are needed as previously discussed. Deconvolution analysis can be used to find the true mean transit time, by dividing the Fourier transform of the observed concentration–time curve by the Fourier transform of the arterial input function (Art(t)), and then taking the inverse transform. Recent data offer hope that NMR imaging may be able to provide arterial input information directly. Even without this approach, arterial sampling techniques analogous to those used by PET can be applied to NMR data. The Central Volume Principle can then be solved for regional blood flow using the measured blood volume and corrected mean transit time.

CONCLUSION

This report has summarized recent developments in the use of MR contrast agents to measure tissue perfusion. Several important approaches, including techniques which use intrinsic flow-related contrast (73, 75), or nonproton markers such as D₂O (76), are discussed by others in this issue. Although each approach offers both advantages and disadvantages, the use of contrast agents to assess tissue microcirculation is likely to be the first put into widespread use, due to the ready availability of agents such as Gd(DTPA)²⁻ and to the high intrinsic sensitivity of MR images to the presence of these compounds. The first applications of these techniques will likely be qualitative, where assessment of even gross abnormalities in cerebral or myocardial perfusion has important clinical impact. With careful additional study, these tech-
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techniques should become capable of providing quantitative as well as qualitative assessment of tissue microcirculation. In this setting, the well-established high spatial resolution and recently established temporal resolution of MR imaging offer the potential for the most detailed in vivo mapping of tissue microcirculation yet available. The use of such tools for clinical assessment and physiological research will increase our knowledge of normal and pathologic human function.

REFERENCES