Water Diffusion and Exchange as They Influence Contrast Enhancement

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The contrast-enhanced magnetic resonance imaging (MRI) signal is rarely a direct measure of contrast concentration; rather it depends on the effect that the contrast agent has on the tissue water magnetization. To correctly interpret such studies, an understanding of the effects of water movement on the magnetic resonance (MR) signal is critical. In this review, we discuss how water diffusion within biological compartments and water exchange between these compartments affect MR signal enhancement and therefore our ability to extract physiologic information. The two primary ways by which contrast agents affect water magnetization are discussed: (1) direct relaxivity and (2) indirect susceptibility effects. For relaxivity agents, for which T1 effects usually dominate, the theory of relaxation enhancement is presented, along with a review of the relevant physiologic time constants for water movement affecting this relaxation enhancement. Experimental issues that impact accurate measurement of the relaxation enhancement are discussed. Finally, the impact of these effects on extracting physiologic information is presented. Susceptibility effects depend on the size and shape of the contrast agent, the size and shape of the compartment in which it resides, as well as the characteristics of the water movement through the resulting magnetic field inhomogeneity. Therefore, modeling of this effect is complex and is the subject of active study. However, since susceptibility effects can be much stronger than relaxivity effects in certain situations, they may be useful even without full quantitation.

Index terms: Water diffusion • Exchange • Contrast agents • Perfusion • Relaxation

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Abbreviations: EPI = echoplanar imaging, Gd = gadolinium, Gd-DTPA = gadolinium-diethylenetriamine penta-acetic acid, MBF = myocardial blood flow, MR = magnetic resonance, MRI = magnetic resonance imaging, NMR = nuclear magnetic resonance, PS = permeability surface area product, SNR = signal-to-noise ratio.

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CONTRAST AGENTS SERVE several purposes in magnetic resonance imaging (MRI), as they do in most diagnostic imaging modalities. In general, they are used to provide physiologic information—eg, tissue perfusion, blood volume, the status of the blood-brain barrier, leakiness of breast tumors—by creating changes on the magnetic resonance (MR) images due to the arrival and accumulation of contrast agent focally in the tissue of interest. However, unlike nuclear medicine and x-ray studies, changes in MR signal in biological systems rarely provide a direct measure of contrast agent concentration. Instead, changes in the MR image intensity depend on the effect that the contrast agent has on the magnetization of the water in the tissue. Contrast agents affect water magnetization in two primary ways: (1) through direct relaxivity effects and (2) through indirect susceptibility effects. In both cases, water movement determines the effect of the contrast agent in altering water magnetization.

Direct relaxivity effects result when the water molecules enter within the immediate hydration sphere of the agent. Within a fluid compartment that contains contrast agent, water molecules diffuse in and out of the influence of the contrast agent molecules. In addition, tissue is by nature compartmentalized with some tissue compartments that contain contrast agent and some without. However, due to the exchange of water molecules between compartments, the magnetization of water protons in compartments without contrast agent can also be affected by the contrast agent.

Susceptibility effects are due to water movement within magnetic field gradients created by compartmentalized contrast agents. As above, in tissue, this water movement includes both diffusion of water within compartments and exchange of water between compartments.

Therefore, water diffusion and exchange play key roles in determining the contrast agents' influence on water magnetization for both relaxivity-based and susceptibility-based contrast effects. To be able to correctly interpret MR contrast agent studies, an understanding of the effects of water movement on the MR signal is critical. In this review, we discuss how water diffusion within the biological compartments and water exchange between these compartments affect MR signal enhancement and affect our ability to extract physiologic information from contrast agent studies.

Although most contrast agents can be used to produce both relaxivity and susceptibility effects, in general one effect dominates, depending upon contrast agent concentration, MR imaging techniques, and tissue distribution properties. For this reason, and since water movement affects relaxivity-based and susceptibility-based changes differently, the effect of water diffusion and exchange on relaxivity and susceptibility-based contrast enhancement is considered separately. The effect of water movement on

the interpretation of relaxivity agent contrast enhancement is discussed in detail. The effect on susceptibility agent contrast enhancement is extremely complex and is still the subject of active study; hence, its discussion is left for a separate review. We will demonstrate that ignoring the effects of water diffusion and exchange can lead to gross misinterpretation of contrast-enhanced MRI studies.

• RELAXIVITY AGENTS

Relaxivity contrast agents are designed to affect the T1 and T2 relaxation characteristics of the system under study, such that physiologic information can be inferred from administration of contrast agent and subsequent measurement of the system relaxation times. In this section, we will first describe how contrast agent affects the tissue relaxation characteristics and, in particular, how water diffusion and exchange affect this relaxation. The diffusion and exchange time constants of water in physiologic systems will then be presented, followed by experimental issues that must be taken into account when using contrast agents and measuring relaxation times, and finally the impact of these issues on inferring physiologic information will be discussed.

Low doses of paramagnetic agents, such as the commonly used lanthanide, gadolinium (Gd), induce T1 and T2 relaxation through electron-nuclear dipolar interactions. These interactions take place only when the water molecules enter within the immediate hydration sphere of the paramagnetic ion (1). However, water molecules are in constant motion (so-called Brownian motion) and thus diffuse into and out of the hydration sphere of any given Gd molecule rather rapidly. To give some sense of typical water diffusion rates, for a 1 mM solution of gadolinium diethylenetriamine penta-acetic acid (Gd-DTPA), it takes an average of about 3 μsec for water to diffuse from one Gd-DTPA molecule to another, and, neglecting any chemical binding, far less time to diffuse out of the hydration sphere of a given Gd-DTPA molecule. Thus, in the times relevant for MR (millisecond to second), an average water molecule will, in the absence of other hindrances, be in the hydration sphere of a Gd ion thousands or millions of times. When water can freely diffuse this way, the relaxivity effect of the contrast agent concentration [C] on the T1 relaxation of the water can be expressed as (1):

$$\frac{1}{T1_C} = \frac{1}{T1_o} + R1\,[C] \qquad (1)$$

where $1/T1_C$ is the T1 relaxation rate in the presence of contrast agent, $1/T1_o$ is the precontrast relaxation rate, and R1, given in ($mM^{-1}sec^{-1}$) is the longitudinal or T1 relaxivity, a value that characterizes the efficiency with which an agent enhances water relaxation. For example, for Gd-chelates in any of their commercial formulations, the relaxivity R1 at 1.5 T is about 4 $mM^{-1}sec^{-1}$.

For most contrast agents, there is a comparable relaxivity effect on T2 as well:

$$\frac{1}{T2_C} = \frac{1}{T2_o} + R2\,[C] \qquad (2)$$

where R2 is the transverse relaxivity, of the same order of magnitude as R1. For example, with the small Gd chelates at 1.5 T, this R2 is close to 7 $sec^{-1}mM^{-1}$. Though the R2 and R1 are roughly equal, contrast-enhanced T2 changes have a much smaller effect on the signal since, in most biological tissues, the precontrast T2 relaxation rates are much greater than the precontrast T1 rates. Therefore, the percent change in 1/T2 is much smaller than for 1/T1. The remainder of this section will focus on T1; comparable issues arise for T2.

Within a given compartment in which water is free to diffuse, the effect of the contrast agent is to alter the magnetization of the water in that compartment, which recovers with a new time constant $T1_C$ or $T2_C$.

In many biological cases, all of the water in the system is not freely diffusible within reach of the contrast agent. Instead, barriers exist between compartments with contrast agents (referred to as compartment 'C') and those without (compartment 'NC' for no contrast). An example of this is Gd-DTPA in the blood: Gd-DTPA in the vasculature remains in the plasma space and does not enter the intact red blood cell. When it leaks out of the tissue vasculature (eg, in the breast, heart, or liver, or in the brain when the blood-brain barrier is not intact), it remains in the interstitial spaces and does not enter intact parenchymal cells. However, even though the Gd-DTPA is excluded from certain compartments, it can affect the water magnetization in the noncontrast compartment when water molecules (and therefore nuclear spin magnetization) can move between the compartments. This movement of water between compartments is loosely referred to as water "exchange." The extent of the relaxivity effect will depend on the rate of water exchange between compartments relative to the difference between the relaxation rates of the compartments, as will be described below.

When contrast agent is biologically compartmentalized, the exchange of water between the compartments determines the net effect of the contrast agent on the system.

In the simplest case, water moves so quickly between compartments such that all water protons, regardless of the compartment in which they begin, experience the effects of the contrast agent during the time of the MR experiment. This limit is referred to as "fast exchange." Mathematically, fast exchange occurs when the net exchange rate ($1/\tau$) is much greater than the difference between the compartmental relaxation rates (2):

$$\frac{1}{\tau} >> \frac{1}{T1_C} - \frac{1}{T1_{NC}} \qquad (3)$$

Note that $1/\tau$ is equal to the sum of $1/\tau_C$ and $1/\tau_{NC}$ where τ_C and τ_{NC} are defined as the average lifetimes of a spin within the 'C' and 'NC' compartments.

Under fast-exchange conditions, the tissue magnetization relaxes with one time constant ($T1_t$) whose rate ($1/T1_t$) is equal to the weighted sum of the intrinsic compartmental relaxation rates (the rates that would exist in the absence of proton exchange):

$$\frac{1}{T1_t} = \frac{p_C}{T1_C} + \frac{p_{NC}}{T1_{NC}} \qquad (4)$$

where p_C and p_{NC} are the fractional water populations of the 'C' and 'NC' compartments.

When water moves "fast enough" between biological compartments, the tissue relaxes monoexponentially with a relaxation rate given by the volume-weighted average of the compartments' relaxation rates.

In the case of fast exchange, even though the contrast agent may be confined to a given compartment, its effect is the same as if it were distributed throughout the tissue volume. This can be seen from Equations (1) and (4) in the simplifying case that the initial T1s in the 'NC' and 'C' compartments have the same T1, $T1_o$. In this case, the T1 of the C compartment, which has contrast agent with concentration [C], is given by Equation (1), and the total tissue T1 is then calculated from Equation (4):

$$\frac{1}{T1_t} = p_C\left(\frac{1}{T1_o} + R1\ [C]\right) + \frac{p_{NC}}{T1_o} \quad (5)$$

Since $p_C + p_{NC} = 1$, this can be rewritten:

$$\frac{1}{T1_t} = \frac{1}{T1_o} + p_C\ R1\ [C] = \frac{1}{T1_o} + R1\ [C_t] \quad (6)$$

where tissue concentration $[C_t]$ is equal to the concentration of agent in compartment C diluted by the additional volume of water in compartment NC, $[C_t] = p_C[C]$. With additional independent information, compartmental information can be derived from the average tissue concentration. For example, in the presence of an intravascular contrast agent, $[C_t] = p_b\ [C]_b$, where b represents the blood volume. Therefore, if the concentration of agent in the blood is known, as from a blood sample, the ratio of the average tissue and blood contrast concentrations will enable the determination of the blood volume fraction, p_b.

With fast exchange, although the contrast agent is confined to a single compartment, its effect is the same as if it were distributed throughout the bulk tissue. The resulting average tissue concentration can be used to determine compartmental information if additional compartmental information is available.

When the exchange of water between compartments is sufficiently slow, the magnetization seems to come from two distinct compartments of size p_C and p_{NC}, and there is no "averaging" of the relaxation decay between the two compartments. This regime is referred to as "slow exchange." Mathematically, slow exchange occurs when the net exchange rate $(1/\tau)$ is much less than the difference between the compartmental relaxation rates (2):

$$\frac{1}{\tau} << \frac{1}{T1_C} - \frac{1}{T1_{NC}} \quad (7)$$

With slow exchange, distinct environments exist each with their own time constant:

$$\frac{1}{T1_C'} = \frac{1}{T1_C} + \frac{1}{\tau_C} \quad (8)$$

$$\frac{1}{T1_{NC}'} = \frac{1}{T1_{NC}} + \frac{1}{\tau_{NC}} \quad (9)$$

In this case, a single relaxivity with which to determine the bulk tissue concentration is undefined; that is, Equation 6 is not applicable. However, unlike the fast-exchange case where the signal is independent of exchange, under slow-exchange conditions, the compartmental relaxation rates and therefore signal intensities remain dependent on exchange and, indeed, on the exact nature of the exchange process. This point is typically ignored in the literature where it is assumed that under slow-exchange conditions, the compartmental relaxation rates will equal the intrinsic relaxation rates, a condition that is only exactly satisfied if there is no exchange between compartments. The effect of such assumptions on measurements such as fractional blood volume is discussed below.

In the case of slow exchange, the water magnetization relaxes with multiple time constants. However, these time constants can still be affected by the exchange itself. Only in the total absence of exchange are the time constants equal to the intrinsic time constants.

In between the cases of fast and slow exchange lies "intermediate exchange" where the compartmental relaxation rates and exchange rates have values of the same order of magnitude. This case, of great interest for biological applications, cannot be simply described. Rather, it may be necessary to use a more complete exchange model that describes the MR signal intensity for all conditions of exchange. Such models were developed in the early studies of nuclear magnetic resonance (NMR) in biological systems, first presented by Zimmerman and Brittin (3) and further developed by others (eg, see refs. 2, 4–6), in the simple case that water exchange is completely modeled as a first-order rate constant, $1/\tau$. In that general case, signal intensity from the mixed compartments recovers biexponentially, with time constants and amplitudes that depend on the sizes and relaxation rates of the individual compartments, as well as the exchange rate between compartments. The equation degenerates into the cases of fast and no exchange in the limits where τ is very small and very large, respectively. Although the algebra is straightforward, the explicit equations for the observed time constants and amplitudes are complex and the interested reader is referred to, for example, the derivations in Hazelwood et al (7).

In the intermediate-exchange regime, the description of the MR signal intensity is much more complex but reduces to the fast- and slow-exchange cases in the extreme limits of exchange.

The general exchange models, referred to above, describe the movement of protons between compartments as a first-order exchange process and assume that the diffusion within compartments is fast enough so that all water within a compartment has experienced the same averaged magnetization. Alternatively, Bauer and Schulten (8) formulated a more general model where an averaged compartmental magnetization is not assumed. It therefore takes into account such things as compartment sizes and diffusivities, allowing for the possibility of a distribution of magnetization states and therefore relaxation times within a compartment. Whether it is necessary to consider such effects is discussed below.

In summary, when the condition exists that contrast agent is confined to a single compartment, one must take into account the exchange of water between compartments to determine the effect of the contrast agent on the water magnetization. In the next section, we will consider what these exchange rates are for typical physiologic conditions, and then we will consider the experimental issues relevant to measurement of the tissue T1 in the presence of water exchange. Finally, the implications for measurement of physiologic parameters will be considered.

Physiologic Diffusion and Exchange Rates

In the physiologic situation, several main compartments exist in tissue. Contrast agent can be confined to compartments of different sizes and can move between compartments. However, given the focus of this review, the following discussion will not consider contrast agent movement. Rather, we will examine the relevant time scales for water diffusion and exchange for the case where the contrast agent is well mixed within its compartment of distribution.

Whether water diffusion within a compartment is fast enough so that an averaged compartmental magnetization can be assumed depends on the distance that water can diffuse during the time between excitation of the protons and measurement of the signal (t_m). This distance is given by the mean path length (L), which is a function of the water diffusion coefficient, D and t_m ($L = \sqrt{6D \cdot t_m}$, in three dimensions). In T1 experiments, with t_m on the order of a second and a typical diffusion coefficient for water in tissue of 1.0 μm^2/msec (9,10), L is approximately 80 μm. This distance is much greater than the average

capillary distance of 8 μm and the mean intercapillary distance in, for example, the heart (19–23 μm) and the brain (23.7 μm) (11) and, therefore, greater than the distance the water needs to diffuse within the interstitial and cellular spaces. Consequently, to first order, negligible gradients of relaxation should exist and each tissue compartment should be well described by monoexponential T1 relaxation. Such may not be the case for T2 experiments where T2 and therefore t_m are necessarily much shorter than T1 (on the order of milliseconds). Consequently, for the case of T2 or in cases of pathology where compartmental distances and diffusion coefficients can be quite large or slow, respectively, it may not be correct to assume homogeneous relaxation decay within a compartment. In these cases it may be necessary to utilize models that describe relaxation time distributions within tissue (eg, ref. 8). However, given that under normal physiologic conditions, well-mixed compartments can be assumed for T1 studies, the focus of the remainder of the discussion will be on the exchange of water across compartmental membranes.

As a first-order approximation, water within most biological compartments of tissue diffuses quickly enough within that compartment to be well mixed during the MR measurement time.

Water mobility across intercompartment boundaries, usually cell membranes, can have a much more pronounced effect biologically. Because water mobility is fast within the compartment, the rate of exchange of water *across* a membrane is thus a prime determinant of the average lifetime of a spin within a compartment (τ). In the simplest model, the typical time a proton remains within a compartment depends on the permeability coefficient, P, of the compartmental boundaries, the surface area of the membranes, S, and the volume, V, of the compartmental space:

$$\text{Exchange Rate} = \frac{1}{\tau} = \frac{PS}{V} \qquad (10)$$

For many regular structures, the ratio of volume to surface area of the surrounding membrane is of the order of the linear dimension of the compartment. As an example, red blood cells, which are among the smallest cells, have very small volume-to-surface area ratios, and very permeable membranes. As a result, the value of τ inside red blood cells is ~10 msec, giving an exchange rate on the order of 100 sec^{-1} (12,13). As described above, whether exchange between red blood cells and plasma can be considered fast, slow, or intermediate depends on the value of the exchange rate relative to the compartmental relaxation rates. For a standard 0.1-mmole/kg dose of Gd-DTPA, the first-pass plasma Gd-DTPA concentration may be as high as 5 mM (14), resulting in a maximum plasma 1/T1 of approximately 20 sec^{-1}, at 1.5 T. Since this value is much less than the exchange rate, we can say that, for typical doses of Gd-DTPA, the plasma plus red blood cells are in fast exchange, that is, a fast-exchange model can be used to describe the relaxation of whole blood.

Exchange of water in and out of red blood cells is fast enough such that, with typical contrast agent concentrations used, water is in the fast-exchange regime. Therefore the vascular water magnetization relaxes with one time constant.

Similarly, relaxation studies in isolated, perfused heart preparations indicate that the interstitial/cellular proton exchange rate is between 8 and 27 sec^{-1} (15). These results are consistent with those of Wedeking et al (16), where T1 measurements made in the myocardium of nephrectomized rat hearts (immediately postexcision) suggest an interstitial/cellular exchange rate of about 21 sec^{-1}. Additional studies (17) performed in striated muscle immersed in isotonic solutions of Gd-DTPA are consistent with a higher interstitial/cellular exchange rate of 50 sec^{-1}. Given that interstitial concentrations can reach nearly the same maximum level of plasma concentrations, when extraction is high, the interstitial relaxation rate may reach a value as high as 20 sec^{-1} for a standard dose of Gd-DTPA. Under this condition, since the exchange rates and relaxation rates are comparable in value, the system is in the intermediate exchange regime. However, more commonly, the interstitial concentrations during most of the contrast agent wash-in are lower than this value, so the assumption of fast exchange between the interstitial and intracellular compartments may still be appropriate. However, relaxographic measurements made in yeast cell preparations yielded much lower cellular exchange rates of approximately 1.5 sec^{-1} (18). It is apparent that more information is needed with regard to in vivo exchange rates and optimal contrast doses for modeling of water exchange and hence relaxation phenomenon.

Exchange of water between cellular and interstitial spaces is intermediate to fast for typical doses of contrast agent. Therefore, care must be taken when modeling T1 relaxation phenomenon.

In comparison, exchange of water between the vascular and extravascular spaces is usually much slower than the exchange between the cellular and extracellular spaces within the vascular and extravascular compartments. In particular, the vascular-extravascular exchange rate has been shown to be approximately 1 sec^{-1} for normal brain (19) and less than 7 sec^{-1} for cardiac vasculature (15). These estimates are further supported by capillary permeability surface area product (PS) values found in the literature. For example, measurements of water extraction in isolated perfused rat hearts (20) give PS values of approximately 6 to 35 ml/min per milliliter of tissue for flow rates of 2.5 to 15 ml/min per milliliter of tissue water. Assuming a myocardial fractional blood volume of 0.10 ml/g and using Equation (10), the vascular-extravascular exchange rates are estimated to be 1–6 sec^{-1}. These exchange values are not fast for typical concentrations of contrast agent. Whether the exchange can be considered slow or intermediate warrants further study.

Exchange of water between the vascular and extravascular spaces with typical contrast agent concentrations is in the slow- to intermediate-exchange regime. Therefore, the intra- and extravascular spaces relax with separate time constants.

In general, the tissue can be viewed in terms of four compartments, two cellular compartments (red blood and parenchymal cells) and two extracellular compartments (plasma and interstitium). The intra-/extracellular compartments are typically in fast exchange. This conclusion is made, despite not knowing pre- and postcontrast T1 differences exactly, because cellular PS/volume (V) ratio is typically large, due to both high water permeability and large surface/volume (S/V) ratio. Consequently, in the context of T1 relaxation, the red blood cells and plasma relax as one vascular compartment while the parenchymal cells and interstitium relax as one extravascular compartment. Whether the vascular and extravascular relaxation rates are the same, that is, whether the whole tissue relaxes as a unit depends on the intra-/extravascular exchange. Intra-/extravascular exchange precon-

trast is also usually in fast exchange: in many biological systems (gray and white matter in the brain, heart, kidneys), tissue T1 and blood T1 are fairly close (~1 sec) so that the relative "slowness" of $1/\tau$ is offset by the small difference between the compartmental relaxation rates. In other systems (liver, spleen) that have shorter T1s, the exchange rates appear to be faster (larger permeability because of function) than T1 rate differences, so again we are in fast exchange. However, with the administration of contrast agent, the T1 rate differences become large enough such that the vascular/extravascular exchange can no longer be considered fast in many tissues (brain, heart, kidneys).

In summary, water moves within and between several tissue compartments. Measurements of compartmental diffusion and exchange indicate that the rate-limiting step in water movement typically exists at the boundaries between the compartments. With typical values of contrast agent used physiologically, this water exchange rate can be slow relative to the differences in compartmental relaxation rates, complicating experimental studies and interpretation, as described below.

Experimental Issues

Although the diffusion and exchange of water in physiological systems are functions of the tissue properties, there are several experimental parameters that could affect how the water motion will impact the actual measurement of relaxation phenomena, and hence the interpretation of the data relevant to physiologic information. This section will discuss these experimental issues that must be taken into account when designing and interpreting relaxation data. The following section will present the impact of these issues on the actual measurement of physiologic parameters.

One experimental issue has already been raised, that of choosing a contrast agent concentration for the studies. According to Equations (3) and (7), whether or not a system can be described as being in the fast- or slow-exchange regime depends on the relative values of the exchange rate to the difference between the compartmental relaxation rates. Although the exchange rates are dictated by the physiology, the compartmental relaxation rates depend on the level of contrast, according to Equation (1). Consequently, the level of contrast concentration may alter the exchange regime of the system being measured.

The issue of contrast agent concentration determining the exchange regime is complicated. For example, during a bolus administration of a contrast agent, the compartmental concentrations of an agent such as Gd-DTPA are changing over time. The tissue may be in fast exchange before adding contrast agent, remain in this regime at low concentrations, and enter the intermediate to slow regime as the contrast agent concentration increases. As an example, T1 measurements made in excised, nephrectomized rat hearts and skeletal muscle demonstrated monoexponential T1 decay for concentrations of 143Gd-Gd(HP-DO3A) less than approximately 0.65 mM and biexponential T1 decay for concentrations greater than 0.65 mM (16). One possible interpretation of this result is that for low contrast concentrations, the tissue is in the fast-exchange regime, whereas for higher concentrations, exchange is intermediate to slow between at least two compartments. This is consistent with an increasing difference in the compartmental relaxation rates as the contrast agent is added, while the exchange rate, a physiologic parameter, remains unchanged.

This issue was addressed with computer simulations for the case of myocardial interstitial/cellular exchange (15) in the context of Gd-DTPA washing into the myocardium. It was found that the cellular/interstitial relaxation rate differences remained less than the exchange rate (in the fast-exchange regime) during the entire time course of Gd-DTPA wash-in for a Gd-DTPA dose of less than 0.02 mmole/kg, much lower than the standard dose of 0.1 mmole/kg. For a higher dose, the system may be moving from fast exchange to intermediate or slow exchange. Consistent with these predictions are the results of Wendland et al (21) demonstrating that the dose dependence for both intravascular and extravascular agents was inconsistent with monexponential T1 relaxation, that is, inconsistent with fast exchange throughout the dose range.

The exchange regime of a system depends on the relative values of exchange rate and the difference between the compartmental relaxation rates, which in turn depend on contrast agent concentration. Therefore, interpretation of studies using variable concentrations of contrast agent must take into account the possibility of variable exchange regimes.

Once a contrast agent concentration is chosen, the next experimental consideration is determining a protocol with which to measure the relaxation characteristics of the system. Experimentally, the MR signal is obtained from the water in all tissue compartments (i.e., vasculature, interstitium, and cells all within a given voxel). If the entire system is in fast exchange, then the magnetization from the entire system relaxes with a single time constant, and measurement of this time constant is straightforward.

With intermediate or slow exchange in the system, the system magnetization relaxes with several time constants. How well the measured relaxation time constants reflect the true time constants depends on two main issues. First, the relative amount of magnetization relaxing with the different time constants and the relative values of the time constants will impact how well the individual time constants can be sampled. For example, if the vasculature comprises only a small fraction (eg, 5–10%) of a given tissue volume, then the magnetization will be difficult to detect experimentally if water is in slow exchange with the rest of the tissue. Second, the inversion delays used to sample T1 relaxation will impact how the individual time constants are sampled, an issue discussed in more detail below.

A more important limitation for measuring the true time constants in the system in most contrast agent studies is that a very limited number of data points are acquired during the relaxation of the system. There are two main impacts of the limited sampling of the relaxation curve: First, the number of points acquired is not sufficient for accurately fitting multiple time constants. Therefore, the data are usually forced into a fit of a single time constant, the *apparent* time constant. Second, the apparent single time constant is heavily dependent upon the choice of the sampling times (the inversion delays in a T1 experiment). For example, if the sampling times are long relative to a short time constant, the resulting relaxation will primarily represent the relaxation of the longer time constant. Sampling the entire decay curve so that both long and short time constants are sampled, at least to some degree, will give an apparent relaxation time that will change depending on the list of sampling times chosen. As an example, consider the case where $p_C = 0.1$, $p_{NC} = 0.90$, $T1_C = 200$ msec, and $T1_{NC} = 800$ msec and there is no proton exchange between the compartments. If an inversion recovery sequence is used to sample the decay for a range of inversion times (TI: 0.10, 0.5, 1.0,

3.0, 5.0 sec), the apparent T1 will equal 736 msec. If, however, shorter TI times of 0.005, 0.01, 0.05, 0.10, 0.5, and 5.0 sec are used, the apparent T1 will equal 637 msec, a value that is different by 15%. Results that are so dependent on the design of the experiment can lead to important inaccuracies in the measurement of the parameter of interest.

Note that these "true" time constants that we are trying to accurately measure are not necessarily the same as those that the compartments would have in the complete absence of exchange (ie, the intrinsic time constants), because even slow or intermediate exchange affects the true compartmental time constants, as discussed previously.

In another scenario, if only very short inversion times are used, the apparent T1 approaches that which would exist under conditions of fast exchange ($T1_{fast}$ = 615 msec, in the previous example), despite the fact that the underlying condition is no exchange in this example. In fact, for short enough inversion times, the resulting magnetization does not depend on exchange at all. Intuitively, this corresponds to the notion that at $TI<<\tau$, since there is not enough time for exchange to take place, it cannot have an impact on magnetization, and thus signal. For example, as noted by Hazlewood (7), the initial slope of the signal decay curve is the same for the no-exchange and fast-exchange cases. This concept has been recently used for the measurement of liver blood volume (22) with much less dependence on intra-/extravascular water exchange. More recently, a comprehensive working understanding of the accuracy and precision of such exchange-minimization methods has been presented (23).

In summary, the MR signal is obtained from the water in all tissue compartments. In the case of fast exchange, one time constant exists and is straightforward to measure. With intermediate or slow exchange, the ability to detect multiple time constants, or the value of a single apparent measured time constant, depends critically upon the relative amount of magnetization of the time constants and the choice of experimental parameters.

Impact on Physiologic Parameters

When physiologic experiments are performed, an assumption is usually made that the exchange of water between various compartments is either fast or slow. The impact of these assumptions is different depending upon the physiologic parameter of interest. In this section, we will discuss the effect of assuming fast and slow proton exchange on the determination of compartment sizes (cellular/extracellular, blood volume) and perfusion. This will be followed by a brief discussion of methods that do not make such assumptions, those that minimize the exchange dependence, or those that incorporate exchange into the analysis of the measurements.

For the cases where multiple time constants are detectable, much effort has been invested to relate the magnitude of the observable components to the size of physiologic compartments. An example of this is skeletal and cardiac muscle where two time constants are observable (7,16,24) both before and after the administration of an extracellular contrast agent. As the contrast concentration is increased, only one of the time components is affected, suggesting that this time constant is that of the extracellular space. However, the relative magnitudes of the time constants did not represent the relative fractions of the cellular and extracellular spaces. This results from the fact that how well the observable fractions and relaxation times represent the true physiologic fractions and intrinsic time constants depends on the rate of proton exchange between the compartments. In fact, only in the complete absence of exchange are the observable fractions and relaxation times simply and directly related to the physiologic fractions and intrinsic relaxation times. This point was well described in the studies of Mulkern et al (25).

Only in the true slow exchange (not intermediate exchange) case are the fractional magnitudes of multiple time constants equal to the fractional sizes of physiologic compartments.

Many MRI studies have been undertaken to evaluate tissue blood volume fraction (p_v) with long-lived intravascular T1 contrast agents. Typically, in such studies, the issue of vascular-extravascular proton exchange is taken into account by determining the fractional blood volume in one of two limits of water exchange: from the T1 relaxation rate assuming fast proton exchange (26–28) or MR signal intensity differences assuming no proton exchange (29,30) between the vascular and extravascular spaces. Given that recent results indicate that the vascular exchange is not fast for typical doses of contrast agent, a recent study addressed the issue as to whether the simple exchange models can be used to accurately measure blood volume (23). Computer simulations demonstrated that when using either the no- or fast-exchange models, the vascular volume fraction can be substantially overestimated or underestimated, respectively. T1 and signal intensity measurements made in a rat model demonstrated that these theoretical findings are biologically relevant and that simple exchange models may result in blood volume measurements that are strongly dependent on the experimental parameters.

Of particular note in these studies were the results of the simulations for the case of no exchange. Specifically, as the vascular contrast concentration increased, the overestimation of the blood volume estimate increased. This result seems surprising considering that the slow-exchange condition (Equation [7]) is better satisfied with higher contrast concentrations. However, as the slow-exchange limit is approached, while the time constant magnitudes approach the physiologic compartment sizes, the apparent time constants themselves do not. In particular, even under slow-exchange conditions, the observed relaxation rates still depend on exchange. As a result, under slow-exchange conditions and assuming the blood compartment is completely relaxed, the calculated p_v approaches a value that is dependent on the exchange rate and TI, when using an inversion recovery sequence:

$$p_v \text{ (calculated, slow)} = p_v \text{ (true)} \left(1 + \frac{TI}{\tau}\right) \qquad (11)$$

Thus, a longer TI allows more time for vascular spins to enter the extravascular space and be affected by the contrast agent, a condition which appears as a larger apparent vascular space.

Similarly, the results of the fast-exchange model estimates also depend on the correctness of the exchange assumptions. As contrast concentration is increased, the fast-exchange assumption (Equation [3]) is less well satisfied and the measurement becomes increasingly inaccurate. For high concentrations, the limit that the blood volume estimate approaches also depends on the TI value (23).

Even with an intravascular contrast agent, the measurement of blood volume can be grossly overestimated or underestimated if the slow- or fast-exchange model is assumed.

A common approach to the evaluation of perfusion is to image the first-pass bolus of an extracellular contrast

agent such as Gd-DTPA (eg, see refs. 31–37) or an intravascular agent such as polylysine-Gd-DOTA (38). In these studies, it has been assumed that greater regional blood delivery leads to a higher local concentration of agent, resulting in a more pronounced T1 effect (shortening) and a higher signal (assuming a T1-weighted imaging sequence). However, the assumption that a direct relationship exists between tissue agent concentration and T1 enhancement is equivalent to assuming fast proton exchange between all tissue compartments. Inconsistent with this assumption are the results of Wendland et al (21) who used an inversion recovery echo-planar imaging (EPI) sequence to dynamically monitor the first pass of intravascular and extravascular contrast agents through normal rat myocardium. They found that the profile of dose dependence for both agents was inconsistent with monoexponential T1 relaxation. Similarly, Judd et al (39) measured tissue T1 in isolated nonbeating canine septa using both intravascular and extracellular T1 contrast agents. They also found that peak change in myocardial R1 scaled nonlinearly with perfusate concentration, a finding inconsistent with fast water exchange between all compartments. This again demonstrates that T1 enhancement in myocardial tissue can be strongly affected by myocardial water exchange for both intravascular and extracellular MR contrast agents.

Given the measurements described above, which suggest that the vascular-extravascular exchange is not fast, the question was raised as to whether the fast vascular-extravascular exchange assumption would lead to serious errors in the interpretation of perfusion studies (15). It was found that for blood volume fractions of 12.5% and steady-state whole blood concentrations of Gd-DTPA up to 8 mM, the true tissue Gd-DTPA concentration could be underestimated by as much as 20%. In general, the error scaled with the blood volume fraction, so for most tissues where the blood volume is less than 10%, the error should be less than the 20% listed here. It must also be noted that this calculated error is also dependent on the measurement parameters and choice of contrast concentrations.

Perfusion measurements can similarly be off by up to 20%, depending on the experimental conditions and modeling assumptions.

What is currently needed is a better understanding of when and at what error level these exchange issues are relevant. For example, Wilke and coworkers (38) demonstrated that, when using an intravascular T1 contrast agent, there is excellent agreement between MRI and radiolabeled measurements of regional myocardial blood volume and flow. However, the region-to-region ratio of MR myocardial blood flow (MBF) to microsphere-measured MBF was 0.9 ± 0.4. That range of variation could easily hide the effects due to exchange assumptions or other errors due to inaccurate estimates of input data.

As mentioned previously in the experimental issues section, a measurement can be made minimally-dependent on exchange if the signal enhancement curves are sampled at times that are short relative to the relevant time constants of the system (compartmental relaxation times and time to reach equilibration (in short-TR sequences) (7,23). For example, when measuring blood volume, short TI or short TR methods can be used to make measurements of blood volume that are minimally dependent on exchange (22,23). However, with such methods, there is a trade-off between the accuracy (short sampling times and thus minimal exchange dependence) and precision (low signal-to-noise ratio [SNR] at short sampling times). These issues are discussed in detail elsewhere (23). Similarly, perfusion studies, such as those described above, can be made minimally sensitive to exchange by measuring the signal at a fixed short TI (or TR), which is much less than the shortest expected compartmental T1, as contrast agent washes in.

Alternatively, to avoid the necessity of having to assume limits of exchange, or carefully considering sampling times for exchange minimization, it may be possible to derive the desired physiologic parameters by fitting relaxation data to the general exchange equations such as those described elsewhere (7). However, the difficulty with such multiparameter, nonlinear fits is the possibility of a large covariance between the fitted parameters: that is, trade-offs between several parameters such that physiologically incorrect values result in a good fit of the data. However, with the appropriate pulse sequence and sufficient signal to noise, a full fit for the desired parameters may prove to be a feasible approach (eg, see ref. 40).

In summary, assuming purely fast or slow exchange can lead to significant errors in the prediction of physiologic parameters. One option is to understand when and at what level these exchange issues are relevant, and interpret the data accordingly. Methods can be used to minimize the effects of exchange on the physiologic measurements. Alternatively, the relaxation may be fit to the general exchange equations.

• SUSCEPTIBILITY AGENTS

A second type of contrast agent is susceptibility agents. These agents introduce local magnetic field inhomogeneities in the system, which subsequently enhance T2 relaxation. There are two related mechanisms by which MRI contrast can be produced from such local magnetic field heterogeneity. First, as protons diffuse through the microscopic magnetic field inhomogeneities, the protons lose phase coherence due to their Brownian random walks through the inhomogeneous magnetic field. In addition, even without the movement of water, the magnetic field inhomogeneities and therefore heterogeneity of frequencies within an imaging voxel can affect the signal intensity (in gradient echo images) by causing intravoxel dephasing.

For contrast agent–based susceptibility contrast, the strength of the magnetic field inhomogeneities is directly proportional to the agent's magnetic susceptibility (χ), but the exact magnitude and distribution of the field inhomogeneities depend on the size and shape of the contrast agent as well as the size and shape of the contrast agent–containing biological compartment (41). In addition to the susceptibility of the chosen contrast agent, the magnitude of the susceptibility-induced relaxation effect will depend on how water moves through the tissue, and therefore how it samples these field inhomogeneities. In real biological systems, these effects are extremely complex to predict and understanding these effects in MRI is an ongoing research endeavor (eg, see refs. 8, 42–46).

While the underlying contrast mechanisms are complicated, one potential strength of susceptibility agents is that they tend to be more sensitive than direct relaxivity agents for several physiologic measurements. One example, is in the measurement of blood volume and flow using intravascular agents (eg, see ref. 47). As we discussed above, intravascular relaxivity agents are typically in the slow-exchange regime for T1 at high concentration, so the signal change they can produce is limited typically to changes on the order of the blood volume fraction, which in many organs is less than 5%. Susceptibility agents, on the other hand, potentially affect all protons in the tissue, regardless of water exchange, by producing

magnetic field inhomogeneities that extend into the extravascular space. As a result, especially for small volume fractions and slow transcompartment exchange, one often finds larger effects (ie, more protons affected, greater change in magnetization) from susceptibility agents. However, these larger effects come at the cost of greater uncertainty in the underlying biological interpretation of those changes.

Susceptibility agents introduce local magnetic field inhomogeneities into the system that are dependent upon the contrast agent size and shape and the compartment size and shape. The effect of the inhomogeneities on the system depends upon the water movement through these inhomogeneities. The resulting effects are complex to model; however, their large magnitude may be advantageous for studies of certain physiologic parameters.

• SUMMARY

Administration of contrast agent is used as a means of obtaining physiologic information such as blood volume and perfusion. To obtain this information, the arrival times and concentration of the contrast need to be known in the tissue of interest. This information is derived from T1 and T2 measurements or from the effect of the altered T1s and T2s on signal intensity. For relaxivity agents, both T1 and T2 are affected; however, T1 effects tend to dominate. For susceptibility agents, the effect of the contrast agent is on T2 or T2*, inferred from spin echo or gradient echo measurements.

Relaxivity agents work by affecting water in the hydration sphere of the contrast agent. Although relaxivity agents affect both T1 and T2, T1 effects usually dominate and are the focus of the rest of this summary. Although one would like to calculate the contrast agent concentration from a measurement of T1, in practice, the contrast agent is compartmentalized and water movement within and between compartments affects the T1 of the system. Hence, calculating contrast agent concentration from T1 requires knowledge of the effect of the compartmentation and water movement.

Diffusion of water within a compartment is usually fast enough in physiologic situations such that all of the water has uniform MR relaxation characteristics. If two compartments have different relaxation characteristics due to one containing contrast agent, for example, and if water exchanges between compartments, it is possible for the water to effectively transmit the effects of the contrast agent to other compartments. The effect depends on the rate of exchange relative to the difference in the relaxation rates between the two compartments. If exchange is fast, the relaxation characteristics of the two compartments average. If exchange is slow, more than one relaxation time constant will exist. In tissue, water exchange between the red blood cells and plasma and between the interstitial and intracellular compartments is usually fast for typical contrast agent concentrations, and thus there exists one vascular and one extravascular relaxation time constant. On the other hand, exchange between the interstitial and intravascular compartments can be in the slow- or intermediate-exchange regime, thereby giving rise to at least two time constants that depend on the intrinsic intravascular and extravascular time constants and the actual value of the exchange rate.

Although water exchange is a function of the tissue properties, there are several experimental parameters, including contrast concentration and sampling times that could affect how the water motion will impact the actual measurement of relaxation phenomena, and hence the interpretation of the data relevant to physiologic information. In addition, methods can be used to minimize the effects of exchange on the physiologic measurements, or the relaxation may be fit to the general exchange equations. Although these issues were briefly introduced here, what is currently needed is a better understanding of when and at what error level these exchange issues become relevant.

Susceptibility contrast agents affect the magnetization of the protons in the region of the contrast agent by creating magnetic field inhomogeneities. The MR signal intensity is affected by water moving through these magnetic field inhomogeneities, which induce a loss of phase coherence and this enhances transverse relaxation. Even without the movement of water, these magnetic field inhomogeneities would affect the signal intensity on gradient echo images by causing intravoxel dephasing.

The actual magnitude of the effect of the susceptibility agent depends on the size and shape of the susceptibility agent, the size and shape of the compartment in which it is confined, and the movement of water through the resulting magnetic field inhomogeneity. Thus, modeling the effect is extremely complicated and is still under active study. However, the susceptibility agents potentially can have a much stronger effect than relaxivity agents for certain studies. Methods are currently growing to exploit both relaxivity and susceptibility agents, and only time will tell whether one or both approaches are most appropriate for a given physiologic measurement.

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