Three major models (from Tofts, Larsson, and Brix) for collecting and analyzing dynamic MRI gadolinium-diethylene-triamine penta-acetic acid (Gd-DTPA) data are examined. All models use compartments representing the blood plasma and the abnormal extravascular extracellular space (EES), and they are intercompatible. All measure combinations of three parameters: (1) $k^{psp}$ is the influx volume transfer constant ($\text{min}^{-1}$), or permeability surface area product per unit volume of tissue, between plasma and EES; (2) $v_e$ is the volume of EES space per unit volume of tissue ($0 < v_e < 1$); and (3) $k_{ep}$, the efflux rate constant ($\text{min}^{-1}$), is the ratio of the first two parameters ($k_{ep} = k^{psp}/v_e$). The ratio $k_{ep}$ is the simplest to measure, requiring only signal linearity with Gd tracer concentration or, alternatively, a measurement of T1 before injection of Gd ($T_{1,0}$). To measure the physiologic parameters $k^{psp}$ and $v_e$ separately requires knowledge of $T_{1,0}$ and of the tissue relaxivity $R_1$ (in vitro value).

Index terms: Gd-DTPA Dynamic MRI - Tracer kinetics - Permeability - Extravascular extracellular space - Rate constant

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Abbreviations: EPI = echoplanar imaging, EES = extravascular extracellular space, Gd-DTPA = gadolinium-diethylenetriamine penta-acetic acid, MTGA = multiple time graphical analysis, PET = positron emission tomography, PS = permeability and surface area product.

The aim of this review is to reconcile the various models and to show the relationship (if any) to physiologic variables. Armed with this review, the reader can critically assess publications related to dynamic gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA) MRI. With appropriate MRI technique, these physiologic variables ($k^{psp}$, $v_e$, and $k_{ep}$) can be measured with good absolute accuracy, providing a result independent of the particular observer, MRI sequence, scanner, or site used. These can then be used to study normal physiology (in cases where the blood capillary is permeable) and disease progression and its response to therapy.

The review focuses on Gd-DTPA tracer; however the tracer kinetic principles can be applied to other tracers (eg, blood pool agents [1,2]), provided an appropriate plasma curve $C_p(t)$ is used, although different imaging strategies might be appropriate, since the requirements for temporal resolution are lower. Initial applications were in multiple sclerosis lesions, followed by the retina; more recent applications are in high permeability tumors, where some questions still remain concerning the effects.
of incomplete mixing in the early phase after injection and of flow-limited leakage.

The mixing phase, during which the injected bolus is mixing into the blood plasma and other closely coupled compartments, lasts up to about 2 minutes. Bolus tracking during this phase has been used to measure blood volume, using T2*- or T1-weighted sequences (3,4). This phase cannot be described properly using compartmental analysis and is not considered in this review. However, if the local arterial input function (ie, plasma concentration) can be measured, it may be possible to characterize leakage in the surrounding tissue during this early phase.

Early Models

Early work in tracer kinetics, before the advent of noninvasive in vivo imaging, was carried by physiologists using radioactive tracers in animals that were then killed to measure the tracer concentration in the tissue of interest (5). The application of diffusion theory to the transport of tracers across a capillary wall and the knowledge that the flux (flow rate) is proportional to the concentration gradient led to the notion of a permeability constant $P$ (6,7), defined as the flux (m mole sec $^{-1}$ or mmole min $^{-1}$) per unit concentration difference and per unit area of semipermeable membrane:

$$\text{flow of tracer} = P \cdot S \cdot \Delta C \cdot M_i$$  

(1)

where $S$ is the area of the membrane per unit mass of tissue (cm$^2$ g$^{-1}$), $\Delta C$ is the concentration difference (m mole cm$^{-3}$) across the membrane, and $M_i$ is the mass of the tissue concerned. (The total area of the membrane is thus $S \cdot M_i$.) The units of $P$ are therefore cm min $^{-1}$ or cm sec $^{-1}$. Since $S$ is usually unknown, physiologists often report the product of permeability and surface area per unit mass of tissue (7) (the ‘PS product’; cm$^3$ min$^{-1}$ g$^{-1}$ or cm$^3$ sec$^{-1}$ g$^{-1}$).

In early animal investigations, the PS product of permeable capillary beds was found by injecting tracer into the arterial blood supply, using either an infusion (7) or a bolus (8). The proportion of tracer that left the bloodstream and entered the tissue in one pass of blood through the capillary bed was called the ‘extraction fraction’ $E$ and is related to PS by:

$$E = 1 - e^{-PS/F}$$  

(2)

where $F$ is the capillary blood flow per unit mass of tissue (mL min$^{-1}$ g$^{-1}$). Backflux into the capillary was ignored (ie, the extravascular concentration remained low). If the permeability is high enough to extract most of the tracer in one pass, then the extraction fraction is close to unity (PS $\approx$ F, $E \approx 1$) and PS cannot be determined (since transport across the membrane is then flow limited and independent of PS). The venous concentration is then considerably less than the arterial concentration, and the concept of a well-mixed plasma compartment does not apply. On the other hand, if extraction is low, the flow is sufficient to replace tracer lost by transport through the capillary wall and the blood plasma compartment has a well-defined concentration. PS is then equal to $EF$ (if $E \approx PS/F$).

In 1978, Ohno, Pettigrew, and Rapoport, at Baltimore and Bethesda (9), published a two-compartment model for the distribution of $^{14}$C-labeled compounds of low molecular weight between the plasma and the brain in rats after a bolus injection. This has all the essential elements of later MRI-based models, although the later MRI workers were probably unaware of this work at the time. A dimensionally corrected version of their equations is presented here. The plasma concentration ($C_p$) was represented as the sum of $n$ decaying exponentials (typically three), which were determined from blood samples:

$$C_p(t) = \sum_{i=1}^{n} A_i \cdot e^{-m_i t}$$  

(3)

The tracer uptake in the EES in unit mass of tissue is (taking account of backflux and assuming $PS/F$, and that the plasma volume is small):

$$\frac{dC_t}{dt} = PS \cdot \rho \left( C_p - \frac{C_t}{V_p} \right)$$  

(4)

where $C_t$ is the tissue concentration, $\rho$ the tissue density,
and \( v_e \), the EES per unit volume of tissue. In this equation, the extracellular concentration \( C_e = C_i/v_e \), and the concentration difference \( C_i - C_e \), is driving transport of tracer across the capillary wall. The term 'extravascular extracellular space' (also called the 'interstitial water space') is used here to specifically exclude the blood plasma space (which is technically part of the whole extracellular space). Note that some workers have referred to the EES as the 'extracellular space', even though the latter technically includes the blood plasma. The solution to the differential Equation (4) for the tissue concentration is:

\[
C_i(t) = PS \rho \sum_{i=1}^{n} A_i e^{-\frac{pS\rho_i}{v_e}} - e^{-\frac{m_i}{v_e} (PS/p)}
\]

and measured values were fitted to this model on a PDP10 computer (Digital Equipment Corporation (DEC), MA) to obtain \( PS \) and \( v_e \). At early times (when backflux can be ignored),

\[
PS = \frac{C_i}{\rho \int_{0}^{t} C_e(t') dt'}
\]

Note that these authors (and several others) have confused themselves by measuring tissue concentration per unit mass, whereas blood concentration was per unit volume. As a result, their original versions of Equations (4-6) are dimensionally incorrect (they assumed the tissue density \( \rho \) is dimensionless and equal to 1) and physically incorrect for any density other than 1 g ml\(^{-1}\). In this review, all concentrations are measured per unit volume, since MRI is sensitive to the amount of tracer per voxel (whereas in early animal experiments, the amount of tracer in a known mass of excised tissue was measured). Flow (\( F \)), PS product (\( P \)), and surface area (\( S \)) are still defined per unit mass for consistency with previous published physiologic work.

In 1983, Patlak et al. (10) published a generalized analysis of tracer compartments and a graphical method (multiple time graphical analysis (MTGA)) for determining \( PS \) from the initial uptake portion of the curve: this has the benefit of not requiring computer fitting. However backflux is ignored (the flux is considered unidirectional) and only the early part of the enhancement curve can be used. There is a danger of underestimating \( PS \) (depending on whether data collection continues into the period when the tissue concentration has risen high enough to produce significant backflux into the capillary). This method was used in MRI studies of rat gliomas (11-13). Their measurements of 'blood-to-tissue transport constant \( K_e \) are PS values in units of ml kg\(^{-1}\) min\(^{-1}\), Ianotti et al (14) developed a similar method for application to positron emission tomography (PET) measurements.

Ott et al. (15a) published a general expression in 1991 for leakage of \(^{68}\)Ga-EDTA in brain tumors, which takes account of backflux and of tracer in the plasma:

\[
C_i(t) = \rho K_e (1 - v_e/(1 - Hct)) \int_{0}^{t} C_e(t') e^{-k_b t'} dt' + v_p C_p(t)
\]

(the original equation has been corrected for dimensional errors related to \( \rho \). \( k_b \) is called the "outflux constant"; \( v_p \) is the plasma volume (0 < \( v_p < 1 \)). Estimates of \( K_e \) and \( v_p \) were determined from the early part of the curve, whereas extending data collection beyond 40 minutes enabled \( k_b \) to be determined. Hawkins et al (15b) published a similar expression before Ott, including the presentation of the tissue concentration as the convolution of the plasma concentration with an exponential decay impulse response. However, the work is focused around PET measurements, and an apparent error in the dimensional treatment makes it inapplicable to MRI. Yeung (16) used a similar expression for CT measurements of \( K_e \) and \( v_e \) in brain tumors.

**General Assumptions in any Model**

All of the models described here make some basic assumptions related to concepts in tracer kinetics and NMR theory. These include the following (10):

1. **Compartments** exist that contain the well-mixed tracer in a uniform concentration throughout the compartment.

2. **Linear intercompartment flux**, i.e., the flux between compartments is proportional to the difference in the concentrations in the two compartments.

3. **Time invariance**, i.e., the parameters describing the compartments are constant during the time that data are acquired.

4. **Blood plasma** compartment, with tracer concentration \( C_p \) (units mM or mmol liter\(^{-1}\)).

5. A lesion EES compartment, with tracer concentration \( C_e \) and volume \( v_e \) per unit volume of tissue. This is the space in abnormal tissue to which leaking Gd-DTPA tracer has access and is distinct from the normal extracellular space distributed throughout the body. Strictly speaking, this space into which Gd-DTPA tracer can leak might include spaces other than the EES (eg, intracellular space), although there is no evidence of this. Throughout, it is assumed that tracer in the EES has arrived directly from a nearby capillary; however diffusion through the EES from more distant capillaries is possible and (if present) would render the simple modeling invalid. A simple calculation of the maximum possible size of the effect shows that if diffusion were as free as in pure water (ie, diffusion coefficient \( D = 3 \times 10^{-5} \text{ cm}^2\text{sec}^{-1} \)) and if the EES were large (ie, little hinderance from cells), then in 10 minutes the root mean square distance traveled would be 3 mm. Microscopic circulation within the EES could increase this effect.

6. **Constant relativity**, ie, the increase in NMR T1 relaxation rate is proportional to the concentration of Gd-DTPA tracer:

\[
\frac{1}{T_1} = \frac{1}{T_{10}} + R_f C_i
\]

where \( C_i \) is the tissue concentration, \( R_f \) is the relativity, and \( T_{10} \) is the 'native' T1 (ie, the value of T1 before injection of any tracer).

7. **Fast exchange** of all mobile (NMR visible) protons within the tissue so that the tissue relaxes with a single T1 value, even though the Gd-DTPA is not evenly distributed but concentrated in the EES and the plasma. Although this condition appears true for exchange between cellular and extravascular spaces, the exchange between the vascular and extravascular spaces is probably not fast (17). Thus, when modeling the contribution of Gd-DTPA in the plasma, and particularly when using blood pool agents, errors may arise. The USLSTIR sequence (18) partly overcomes this problem by measuring the longitudinal magnetization in the first 40 msec after inversion, before exchange...
becomes appreciable. More accurate values of plasma volume are then obtained.

**MODELING MRI DATA**

The advent of the clinical use of Gd-DTPA in Japan and Europe from the mid-1980s to probe breakdown in the blood-brain barrier in multiple sclerosis and tumors brought about a flurry of new work studying the dynamics of Gd enhancement. In 1986, Yoshida et al. (19) measured T1 at a range of times after injection, both in plasma and in brain tumors, but there was no pharmacokinetic or physiologic modeling of the data. Three European groups started modeling the signal enhancement as a function of time. These models all apparently developed independently within about 2 years of each other; each had distinct approaches to both data collection and modeling and each spawned rich veins of applications that are still being exploited now. The locations were in London (Tofts and Kermode), Copenhagen (Larsson and coworkers), and Heidelberg (Brix and coworkers).

In February 1989, at the seventh annual meeting of the Society for Magnetic Resonance Imaging in Los Angeles, Tofts and Kermode presented a poster on their new model (20). In a rapidly enhancing multiple sclerosis lesion in brain white matter (reaching its peak at 10 minutes), an influx volume transfer constant (loosely referred to as "permeability") kps of 0.056 min⁻¹ and an EES Vp of 0.18 were measured. A more slowly enhancing lesion (peak at 45 minutes) had lower permeability (kps = 0.012 min⁻¹) and larger EES (Vp = 0.41). These data were included in a published letter (21). Later that year (in August 1989), it was shown at the Society of Magnetic Resonance in Medicine in Amsterdam (22). At the same meeting, Larsson et al. showed their model (23), reporting rate constants kn in acute multiple sclerosis in the range of 0.04–0.11 min⁻¹, compatible with those of Tofts and Kermode (24). Larsson et al. published their full paper on modeling dynamic Gd-DTPA MRI data in 1990 (25) (submitted in April 1989), followed by Tofts and Kermode in 1991 (26) (submitted in June 1989). Brix et al. presented their model in New York in 1990 (26a), and publication followed in 1991 (27).

Table 2 provides a comparison of models.

<table>
<thead>
<tr>
<th>Plasma concentration</th>
<th>Assumed normal (biexponential)</th>
<th>Measured from blood samples</th>
<th>Fitted with single rate constant</th>
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<td>Bolus</td>
<td>Infusion</td>
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<tr>
<td>Can initial rise be</td>
<td>Yes (for kps)</td>
<td>No</td>
<td>No</td>
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Table 2 provides a comparison of models.

**Tofts and Kermode (26) Model**

In the original formulation (20, 22), the permeability P was assumed to be isodirectional (ie, the same in both directions), which is the case for simple diffusive transport. In this case, the flux of tracer from the plasma into the EES compartment is given by Equation (1). However, it is conceivable that there are different permeability constants Ppl and Pout for flux into and out of the EES (eg, if there were active transport mechanisms or differences in diffusion, viscosity, or pressure on each side of the membrane); these are used here for generality. In addition, the treatment is extended here to include the contribution of tracer in the blood plasma to the total tissue concentration. Although this is small (ie, Vp = 0) in blood-brain barrier lesions, it is often significant in tumors. The flux of tracer into the abnormal EES is then (see Equation [1]):

\[ v_p V_p \frac{dC_p}{dt} = (P_{in} C_p - P_{out} C_t) S M_i \quad (9) \]

where Vp and Mi are the volume and mass of tissue being considered (and hence v_p is the volume of EES in that tissue, and the total area is SM). The differential equation describing the tissue concentration is then

\[ \frac{dC_T}{dt} - \frac{dC_p}{dt} = kps \left( C_p - \frac{kps}{v_p} (C_t - v_p C_T) \right) \quad (10) \]

(Note that C_t = v_p C_p + v_t C_T). The volume transfer constant kps has the simple physiologic meaning of being the PS product multiplied by the tissue density (ρ) (ie, kps = ρ Sm). The permeability surface area product per unit volume of tissue (kps = ρ Sm/Vp) or the permeability surface area product per unit mass of tissue (K = PS). It is labeled "PSp" to emphasize that it is the PS per unit volume of tissue and to distinguish it from the rate constants kps, kps, and kps, for example. Under the conditions of small plasma volume (Vp = 0) and isodirectional permeability (ie, kps = kps = kps), this differential equation describing tracer flux is essentially identical to that of Ohno et al (9) (Equation [4]).

The plasma concentration after the injection of a bolus of Gd-DTPA was assumed to be that measured in normal control subjects by Weinmann (29). This was fitted to a biexponential decay (see Fig 1), which is expected from the compartmental theory:

\[ C_p(t) = D \sum_{i=1}^{2} a_i e^{-\lambda_i t} \quad (11) \]

where D is the dose (mmole/kg), and amplitudes a_i are normalized for unit dose (so that C_p is then known for any size dose). The fitted values were a_1 = 3.99 kg/liter, a_2 = 4.78 kg/liter, m_1 = 0.144 min⁻¹, m_2 = 0.0111 min⁻¹. Using this plasma concentration, and solving Equation (10), gives the tissue concentration.
The native T1 of the tissue was measured using a relaxed spin echo and an inversion recovery sequence. Repeated inversion recovery sequences were then run after bolus injection of Gd-DTPA. A straightforward theoretical expression for the signal enhancement (ie, the increase in signal divided by the signal before injection) is a function of the sequence timing parameters (TR, TI, TE) and T1 (which are known), the tissue relaxivity R1 (which was assumed to be equal to that in water) and the tissue concentration (which is the only unknown). Values of kPSp and v, (originally called k and v1) were estimated (assuming that kouTPSP = &s, ie, P, = P,,,, and ignoring plasma volume, ie, vp = 0) with a least-squares fitting program, using Equation (12) and the expression for signal enhancement (see Fig 2). First, note (from Equation [12]) that & cannot be determined independently and, secondly, that v, can only be determined by assuming kouTPSP = kPSp. This equation is essentially identical to that of Ohno et al (9) for isodirectional permeability and vp = 0 (Equation [5]).

In later work, the model was extended in several ways. The initial slope of the signal time curve, before the tissue concentration has risen high enough to cause significant backflux, is proportional to the permeability (26,30; eg, see Equations [6, 9]). The T1 weighting of the sequence signal S can be defined by the time parameter Tk as follows:

\[ T_k = \frac{1}{S} \frac{\partial S}{\partial (1/T_1)} = \frac{\partial E}{\partial (1/T_1)} \]  

where E is the enhancement (the fractional increase in signal). For a spin echo sequence, T1 ~ T1o. The signal enhancement at short times, before the plasma concentration has had time to decrease, is then given by:

\[ E = \frac{S(t)}{S(0)} - 1 = R_1 T_s C_1 = R_1 T_x C_0 (0) [k_{PSp} t + v_p] \]  

where C1(0) is the plasma concentration immediately after bolus injection, and the vp term has been added in this review. Thus, the permeability can in principle be determined from the initial slope.

\[ C_1(t) = D k_{PSp} \sum_{i=1}^{2} a_i^T e^{-\frac{\alpha_{PSp} t}{\mu_i}} - e^{-\frac{\alpha_{PSp} t}{\mu}} + v_p D \sum_{i=1}^{2} a_i^T e^{-m_i t} \]  

The model was applied to leaking capillaries in the retina using spin echo data (31,32). The method for permeability measurement was validated by extracting the vitreous and measuring the amount of Gd-DTPA that had leaked from the retina into the vitreous (31). A comparison of bolus and infusion injections (33) showed that the bolus is usually more efficient at achieving a particular tissue concentration (the exception might be for a short infusion time and a high rate constant kouTPSP/vp). The model fits well to gradient echo data from human breast tumors (34) and to data from implanted human breast tumors (35). Predictions were made of the increased sensitivity to low permeability blood-brain barrier lesions that could be achieved using delayed imaging (up to 2 hours after injection) and repetition time and gradient echo tip angle were optimized (36).

The model has been criticized for its assumption of normal plasma concentration Cp(t). If Cp(t) is known for the particular subject, this knowledge can be used by fitting Cp(t) to the sum of exponentials to determine the plasma parameters aT, and m, (Equation [11]). Alternatively, if Cp is described numerically, a more general solution to the first-order differential Equation (10) is (37):

\[ C_1(t) = k_{PSp} \int_0^t C_p(t') e^{-\alpha_{PSp}/\mu_1(t-t')} dt' + v_p C_p(t) \]  

similar to the expression of Ott (Equation [7]).
**Larsson et al. (25) Model**

Using the extraction fraction concept of Renkin and Cron (see Equation [2]), a differential equation for the tracer flux was obtained, similar to that of Ohno (Equation [5]), except with \( F \) replaced by \( EF \). If the capillary flow is sufficiently high (ie, if \( F > F_s \)), then \( EF = F \) and this is identical to Equation (5). The plasma concentration after injection of a bolus of Gd-DTPA was measured for each patient by taking a series of blood samples and measuring the amount of tracer in each sample (using neutron activation) and fitted to the sum of three exponen-
tials (see Equation [3]).

Two approaches were used to model the signal as a function of Gd concentration. In the simple one, the signal was assumed to be linearly related to Gd concentration: then the signal is related to the permeability by:

\[
S(t) = S(0) + \frac{\dot{S}}{2} \sum_{i=1}^{3} A_i \left( e^{-\frac{EFp}{v_c} t} - e^{-\frac{EFp}{\nu_c} t} \right)
\]

where \( \dot{S} \) is the initial slope of the signal. The measured signal \( S(t) \) was fitted to this expression with only \( EFp/\nu_c \) and \( \dot{S} \) as free parameters. In the more complex approach, the native \( T_1 \) was measured (before injection of Gd) and the relaxation rate \( R, (= 1/T1) \) calculated from the signal at each time point. No assumption was made regarding signal linearity. The relaxation rate is given by:

\[
R(t) = R(0) + \frac{\dot{R}}{2} \sum_{i=1}^{3} A_i \left( e^{-\frac{EFp}{v_c} t} - e^{-\frac{EFp}{\nu_c} t} \right)
\]

where \( \dot{R} \) is the initial slope of the curve. The measured relaxation rate \( R(t) \) was fitted to this expression with \( EFp/\nu_c \) and \( \dot{R} \) as free parameters. Note that the initial slope has been used to 'calibrate' the system so that the relativity \( R, \) is not needed. Nor is the native \( T_1 \) (ie, \( T_{1o} \)) needed in the simple approach (both \( T_{1o} \) and \( R, \) were needed in the Tofts and Kermode model). However, the price paid is the loss of \( k_{PS} \) (or equivalently \( EFp \)); only the ratio of \( EFp \) to \( \nu_c \) is found. These Equations (16) and (17) to determine the rate constant \( EFp/\nu_c \) are comparable with Ohno's Equation (5). In a separate presentation (38), Larsson and coworkers used an in vitro value of relativity \( R, \) and a measurement of \( T_{1o} \) in their model to determine both \( k_{PS} \) and \( \nu_c \) separately.

Myocardial perfusion (ie, blood flow \( F \)) was assessed from the dynamic Gd-DTPA uptake in the myocardium (39-42). The quantity \( EF \) is measured for transport from the plasma (compart-
ment 1) to the EES (compart-
ment 2) is:

\[
\frac{dM_2}{dt} = k_{12} M_1 - k_{21} M_2
\]

where \( M_1 \) and \( M_2 \) are the total amounts of Gd-DTPA in the plasma and the EES, respectively. Setting \( M_1 = C_p \), \( V_p \) and \( M_2 = C_{ES} V_E \), where \( V_p \) and \( V_E \) are the total volumes of the plasma and EES, respectively, using \( V_1 = v_p V_p \), \( V_2 = v_2 V_E \), and comparing with Equation (9), we see the rate constants \( k \) are related to the forward and backward permeabilities \( (P_{in}, P_{out}) \) by:

\[
k_{12} = k_{PS} = \frac{P_{in}}{v_p} = \frac{k_{PS}}{v_p}
\]

\[
k_{21} = k_{ESS} = \frac{P_{out}}{v_2} = \frac{k_{ESS}}{v_2}
\]

where the plasma and EES compartments have been relabeled 'p' and 'e', respectively.

Weinmann's data on the plasma concentration after injection of a bolus of Gd-DTPA (29) were felt to be sufficiently well described during the first 20 minutes by a single exponential decay; first-order elimination from the plasma compartment was therefore used, characterized by a rate constant \( k_{PS} \). The actual injection procedure...
used was a constant rate infusion (typically for 4 minutes), since this could be given in a more controlled way than a bolus. Data collection started just before the start of the infusion and continued after it had ended. An example is shown in Figure 4: the lower curve is still rising after 20 minutes (giving a negative value of \(k_p\): the authors state [27] that this may be caused by transport of tracer from neighboring parts of the heterogeneous lesion and that \(k_p\) is not affected because it is estimated from the wash-in phase of the curve.

The signal enhancement for the SE100/10 sequence was assumed to be proportional to the concentration of Gd-DTPA in the tissue. The signal at any time \(t\) is then

\[
S(t) = S(0) + \frac{A^b}{k_d - k_{ep}} \left[ (e^{k_{ep}t} - 1) e^{-k_{ep}t} \right]
\]

where \(t' = t\) during the infusion, \(t' = t\) (the duration of the infusion) after the infusion, and \(A^b\) is an arbitrary constant. The authors point out that “It is a remarkable property that ... the shape of the temporal response \(S(t)/S(0)\) is determined only by the kinetic parameters \(k_{d1}\) [ie, \(k_{d1}\)] and \(k_{ep}\).” The measured signal \(S(t)\) was fitted to this expression with \(A^b\), \(k_{d1}\), and \(k_{ep}\) as free parameters (see Fig 4).

Note that the ‘calibration’ of the system is contained in the constant \(A^b\) so that once again, as in the Larsson model, the relaxivity \(R_1\) and the native T1 are not needed, and only the rate constant \(k_{d1}\) \(= k_{d1}^{\text{PSV}}/v_c\) is found. The plasma curve was not assumed normal (as did Tofts), nor was it measured directly (as did Larsson), but instead its clearance rate was estimated from the measured tissue curve. After a bolus (ie, \(k_{d1} = 1\), \(k_{d1} = 1\)), this expression reduces to:

\[
\frac{S(t)}{S(0)} = 1 + A^b \left( \frac{e^{-k_{d1}t} - e^{-k_{ep}t}}{k_d - k_{ep}} \right)
\]

which is equivalent to the previous equations of Ohno, Tofts, and Larsson (Equations [5, 12, 16, 17]).

More recently, Hoffmann et al, from the Heidelberg group, have used a fast T1-weighted gradient echo sequence and a reduced infusion length of 1 minute (45). A slightly modified equation was used with a redefined constant \(A\) (here called \(A^a\)). After a bolus injection, the equation reduces to:

\[
\frac{S(t)}{S(0)} = 1 + A^a k_p \left( \frac{e^{-k_{ep}t} - e^{-k_{d1}t}}{k_d - k_{ep}} \right)
\]

Parameter maps of \(A^a\) (as well as \(k_{d1}\)) were considered diagnostic, so it is of interest to know the physical significance of \(A^a\). Shortly after a bolus injection, the enhancement \(S(t)/S(0)\) is \(A^a k_{d1}\) and using the previous expression for the initial slope (Equation [14]), we see that:

\[
A^a \approx R_1 T_1 C_p(0) v_c
\]

Thus, \(A^a\) approximately corresponds to the size of the EES, if the relaxivity, the native T1, and the dose do not vary significantly. Using a similar approach, the original \(A^b\) of Brix (Equation [20]) has the approximate value \(A^b \approx R_1 T_1 C_p(0) k^{\text{PSV}}/v_c\) ie, corresponding to the permeability (provided the relaxivity, \(T_{1p}\), and dose procedure do not alter).

**Other Work**

Buckley et al (46) adapted the Brix model to fit data from breast tumors. \(k_{d1}\) and \(k_{d2}\) were relabeled \(k_p\) and \(k_{d2}\) respectively. After a bolus injection, a fast T1-weighted gradient echo (TR = 12 msec; 128 x 256 matrix) was used. The time between injection and the start of data collection were fitted as free parameters. They pointed out that mixing of the bolus is facilitated by using a saline flush.

Shames et al (2) recorded the signal from tumors, a large blood vessel (the inferior vena cava), and an oil calibration phantom after injection of a blood pool marker (albumin-Gd-DTPA). Using the assumption of signal linearity with Gd concentration, and a public-domain pharmacokinetic modeling computer program, they measured PS and the tissue plasma volume \(v_c\) (47).

Su et al (48a) published a model in 1994 following the same principles as previous workers. A calibration curve was generated using a phantom to convert signal enhancement ratio to Gd concentration; as discussed in the Assumptions section, this curve would be in error since the tissue will have different \(T_{1p}\) from the phantom.

Goward et al (48b) studied brain tumors using echo-planar imaging (EPI). The first passage of the bolus could be observed. Blood samples were taken to measure the plasma concentration. The efflux time constant (ie, \(1/k_{d1}\)) was estimated.

Flickinger et al (49) reported that in breast tumors, the most specific finding for separating benign from malignant lesions was the ratio of maximum intensity change to the time interval for this to be reached. Interestingly, this ratio is approximately equal to the initial slope of the enhancement curve, and thus approximately proportional to \(k_{d1}^{\text{PSV}}\) (Equation [14]). On the other hand, Heierberg et al (50) reported that the peak enhancement has high specificity. For a rapidly enhancing tumor \(k_{d1}^{\text{PSV}}\), using Equations (11) and (12), the maximum tissue concentration \(C_{t,\text{max}} (v_c + v_p) C_p(0)\) and thus gives a good indication of the tumor extracellular space (the sum of the intra- and extravascular components). Therefore, workers may find heuristic tissue enhancement parameters that give...
valuable information, without having related them to changes in the underlying physiologic parameters.

**DISCUSSION**

**Assumptions**

The additional assumptions made by some of the MRI workers are discussed here in more detail.

The plasma clearance parameters $A$ and $m$, are required to characterize the lesion from the tissue concentration. The simplest procedure is to assume they are normal (as Tofts did). The magnitudes of the errors arising from this assumption are still not known, although there has been some theoretical discussion (26,34). There is now a great need to make systematic measurements of plasma clearance curves in control subjects and patients to determine the inter- and intrasubject variability (arising from both physiologic effects and injection procedure) and to determine how this variability propagates into errors in the lesion parameters. In rapidly enhancing lesions, the initial spike in the plasma concentration (39-41) is likely to be important (51) (see Fig 3).

The second option is to measure the plasma concentration. Initially, sequential blood samples were taken (15a,16,25), although this is inconvenient and impractical in a clinical situation. More recently, MRI has been used to observe a major blood vessel (2,18,39-41,47,48b,52). Ideally, this should be the vessel that is directly supplying the tissue of interest; however this requires that a MRI slice can be placed through this vessel: in practice this may be too far removed from the lesion to be imaged simultaneously with it. Some organs may not derive their supply from a single vessel (eg. the breast). Imaging a remote major vessel (eg. the aorta) may give sufficient information, although there may be considerable mixing and dilution of the bolus after being sampled before it reaches the leaking capillary.

The third option, used by Brix, is to estimate the plasma clearance from the tissue curve by including its clearance rate as a free parameter in fitting the enhancement curve, although this prevents $k_{ps}$ from being estimated. This extra degree of freedom may increase the uncertainty in $k_{ps}$; the fitting may be ill-conditioned if the lesion efflux rate constant is low enough to approach the plasma clearance constant ($k_{ps} \approx k_{ps}$ in Equations [20-22]), and there may be a problem in distinguishing $k_{ps}$ from $k_{ps}$ since the equations are symmetric with respect to inter-change of these two fitted variables.

Blood pool contrast agents are much more stable in their concentration, and relatively simple methods may be used to determine their concentration.

The low extraction assumption (see Equation [2]), ie., that flow is sufficient to replace tracer lost from the capillary by leakage (F-PS), is true for permeabilities up to about $k_{ps} = 0.1 \text{ min}^{-1}$ (since typical blood flow is $F = 1 \text{ ml min}^{-1} \text{ g}^{-1}$) and holds for multiple sclerosis lesions (26) and retinal lesions. Tumors and the myocardium may have apparent values of $k_{ps}$ up to 1 min$^{-1}$ (27,34,36,45). Here the extraction is significant, and the tracer flux may be flow limited. In this case, an 'apparent permeability' has been measured, which Larsson et al (25) have shown is equal to EF (see Larsson et al Model section and Equation [16]). Although it is a combination of permeability and flow (see Equation [2]), it is still a physiologic quantity, independent of the MR method used to measure it. By measuring flow $F$ separately (see Other Physiologic Parameters section), it is possible that true PS could be estimated (provided the extraction E does not approach 1).

The in vivo relaxivity $R_1$ has been assumed to be equal to the in vitro value (ie, that in aqueous solution), although the in vitro value can, in principle, be altered in the tissue environment by factors such as temperature, viscosity, binding, reduced water content, and water compartmentalization. The determination of the rate constant ($k_{ps}$) is independent of $R_1$; however $k_{ps}$ will be wrongly estimated if $R_1$ alters from its assumed value. From the linear equation relating signal enhancement and permeability (Equation [14]), it is seen that it is approximately the product ($R_1 k_{ps}$) that is determined. It is unlikely that it will ever be possible to measure the in vivo $R_1$ value in the particular lesion of interest, and currently there is no option but to assume a value for $R_1$ if the permeability is to be estimated. Measurements in vivo in animals in tumors (53), heart tissue (54), and liver (55) give $R_1$ values close to in vitro values, suggesting that the assumption is reasonable.

**Signal or enhancement linearity with Gd concentration** has been assumed by several workers (2,25,27,45,48a). Here the concept is explored in more detail, using a spin echo sequence as an example. The signal from a T1-weighted spin echo, at low concentrations, is

$$S(C) = g PD (1 - e^{-TR(T2,T1,C)T1})$$

$$\approx S(0) + g PD TR e^{-TR(T2,T1,C)T1}$$

$$\approx S(0) + g PD TR R_C (TR, R_C - 1) \text{ (TR, } T2)$$

where $C$ is the concentration (in tissue or a phantom), $g$ is the instrument gain, $PD$ is the proton density, and a Taylor expansion in $x = TR R_C$ has been used. The signal enhancement (ie, fractional increase in signal) is then:

$$E(C) = \frac{S(C) - S(0)}{S(0)} \approx \frac{TR}{1 - e^{-TR(T2,T1,C)T1}} R_C (TR, R_C - 1) \text{ (TR, } T2)$$

Thus the signal increases linearly with concentration, and provided we are on the linear part of the signal versus $1/T1$ curve (ie, $TR, T2$), the constant of proportionality ($g PD TR R_C$) is independent of $T2$, although it does depend on the material slightly through PD (and perhaps $R_1$). In contrast, the enhancement has a constant of proportionality ($R_1 T2$ at small TR) that depends very much on the material. For this reason systems that involve calibration of signal enhancement versus concentration using phantoms are fundamentally flawed.

The dependence of signal on Gd-DTPA concentration can be determined using Ni-DTPA doped gels with tissue-like T1 and T2 values (56). Gd-DTPA added to this substrate has the same relaxivity as in vitro. In contrast, adding Gd-DTPA to aqueous solutions of Mn$^+$ or Cu$^+$ ions gives an altered relaxivity because they bind to excess DTPA.

The more complete treatment of nonlinear signal dependence on T1 (and hence on Gd concentration) is not without pitfalls. A theoretically correct analytic expression for the signal is easily produced; however the system may be nonideal, particularly in having a distribution of tip angles across the slice, which reduces the accuracy of this expression. T1 measurements made using these same expressions can be wildly inaccurate, or very good, depending principally on the slice profile and tip angle accuracy; the same considerations apply to the determination of Gd concentration, even though T1 may not determined explicitly. Ideally, the theoretical expression
should be confirmed with phantoms of known Gd concentration or T1 values.

**Choice of a Model and a Method**

Comparing the equations for tissue concentration for Tofts, Larsson, and Brix (Equations [12, 16, 17, 21, 22]) we can see that all three groups are estimating the same efflux rate constant

\[ k_{psp} = k_{psp}^{\text{max}} \left( \frac{v_c}{v_c^*} \right) = \frac{EF_p}{v_c} = k_p, \quad (26) \]

The actual estimates obtained will differ in the three methods because the plasma concentration is handled differently.

The optimum injection protocol is still open to discussion; however it is likely to be of duration 60 seconds or less (33, 45). Most workers have used bolus injections, since these give useful qualitative information used by radiologists. If the duration is more than about 10 seconds, the center of the injection should be considered the time of the bolus. If enhancement is rapid, the exact time of injection should probably be a fitted parameter (46); otherwise variable and uncontrolled lag times between injection and imaging may be an extra source of variation in the apparent fitted parameters.

The T1-weighted sequence may be a spin echo, gradient echo (2D or 3D), IR-prepared fast gradient echo, or EPI. The choice will depend on what sequences are available, the time resolution and spatial coverage required, and whether sensitivity to low Gd concentrations is required.

The plasma clearance parameters \( A \) and \( m_c \) can be determined in three possible ways (see Assumptions section). MRI measurement in a large vessel is probably the most satisfactory, if it is practically possible.

If a simple analysis is required, \( k_{psp}^{\text{max}} \) can be estimated from the slope of the initial linear portion of the enhancement curve, using Equation (14). \( T_{10} \) can be measured or a normal value assumed. There is no need for nonlinear least-squares curve fitting. The duration of this initial linear portion may be very short (too short to use, as in rapidly enhancing tumors (34)) or can last 10s of minutes (as in retinal lesions (31, 32)).

Following the enhancement curve into the nonlinear time portion enables the efflux rate constant \( k_p = \frac{k_{psp}^{\text{max}}}{v_c^*} \) to be measured (Equations [5, 12, 16, 17, 20, 21, 22]). If the signal increase with concentration is nonlinear, \( T_{10} \) must be measured and used with a theoretical expression for the signal as a function of concentration \( S(C) \) in the T1-weighted sequence. Alternatively, calibration phantoms give an approximate relationship for \( S(C) \) (Equation [24]).

If data from the nonlinear time portion have been collected, they can be used to estimate the influx transfer constant \( k_{psp}^{\text{max}} \) (Equation [12]). \( T_{10} \) is measured or (less satisfactorily) a normal value assumed. The estimate can be refined by improving the knowledge of \( T_{10} \) and the T1 weighting of the sequence. The extravascular extracellular space \( v_c \) can also be estimated (since \( k_{psp}^{\text{max}} \) is already available and assuming the permeability is the same in each direction). Since the EES \( v_c \) can vary with edema, the transfer constant \( k_{psp}^{\text{max}} \) provides a physiologically more relevant measure of the state of the capillary permeability than does the efflux rate constant \( k_p = \frac{k_{psp}^{\text{max}}}{v_c^*} \).

The fitting procedure should determine all the free parameters in a single operation so that all the measured signals are equally weighted and noise is propagated correctly.

**Other Physiologic Parameters**

This review has concentrated on two physiologic parameters that can be determined from analysis of tracer uptake curves: permeability and EES. However, in addition to the native T1, there are two more that can often be obtained in the same MRI examination (making use of the Gd-DTPA bolus) that are particularly relevant if tumors (with increased vascularity) are being characterized and that may add to the physiologic specificity of the examination.

First, the plasma volume \( (v_c) \) (or blood volume) can be determined, either by including a \( v_c C \) term in the tissue concentration (2, 47) (see Equations [7, 12, 15]), if the tissue is sufficiently well vascularized that the contribution from this term is large enough to be determined with good precision. Alternatively, blood volume can be determined by Gd-DTPA bolus tracking (3, 4) using the same bolus that is later to be used to estimate permeability and EES. The size of the plasma space \( v_c \) may possibly predict the capillary surface area \( S \) and thus possibly allowing permeability \( P \) to be estimated (rather than just the PS product). For example the quantity \( (PS/v_c) \) might be relatively independent of \( S \) and \( v_c \).

Second, the blood flow \( (F) \) can be estimated from the transit time of the Gd-DTPA bolus. Alternatively, a separate sequence using arterial spin labeling techniques (which do not require the use of an exogenous tracer) can be used to measure flow. Other MR measurements (PD, T2, magnetization transfer, diffusion, and spectroscopy) may also add to the specificity of the examination.

• **CONCLUSIONS**

With appropriately good techniques of MRI data collection and tracer modeling of the images, physiologic variables can be measured in an objective, reproducible, and noninvasive way. These will have a role in understanding disease process, testing patients in the clinic, and evaluating the effectiveness of new treatments.

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