Review

Estimating Kinetic Parameters From Dynamic Contrast-Enhanced T_1-Weighted MRI of a Diffusable Tracer: Standardized Quantities and Symbols

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We describe a standard set of quantity names and symbols related to the estimation of kinetic parameters from dynamic contrast-enhanced T_1-weighted magnetic resonance imaging data, using diffusable agents such as gadopentetate dimeglumine (Gd-DTPA). These include a) the volume transfer constant K^{trans} (min^{-1}); b) the volume of extravascular extracellular space (EES) per unit volume of tissue v_e ($0 < v_e < 1$); and c) the flux rate constant between EES and plasma k_{ep} (min^{-1}). The rate constant is the ratio of the transfer constant to the EES ($k_{ep} = K^{trans}/v_e$). Under flow-limited conditions K^{trans} equals the blood plasma flow per unit volume of tissue; under permeability-limited conditions K^{trans} equals the permeability surface area product per unit volume of tissue. We relate these quantities to previously published work from our groups; our future publications will refer to these standardized terms, and we propose that these be adopted as international standards. J. Magn. Reson. Imaging 10: 223–232, 1999. © **1999 Wiley-Liss, Inc.**

Index terms: Gd-DTPA; permeability; perfusion; transfer constant; rate constant; extravascular extracellular space

MANY WORKERS have modeled the dynamic enhancement data that can be generated by repeated (dynamic)T_1-weighted imaging of tissue after injection of gadopentetate dimeglumine [previously known as Gd-DTPA (1)] or other Gd-labeled tracers of similar size and pharmacokinetics (2). A set of T_1-weighted images is acquired, (· late phase imaging (50)) starting before a short (bolus) injection, and continued as uptake by the tissue and usually washout from the tissue are observed. The signal in a region of interest (ROI) or pixel can give information about blood flow, capillary leakage, and related physiological parameters. A variety of quantities (some of them physiologic) have been estimated; often the same quantity appears with a different name or symbol in different reports, so that comparison of work from different groups is almost impossible. There is increasing interest in making measurements that are reproducible between different MR centers, and it is now accepted that parameters such as relaxation times, diffusion coefficient, and volume can be measured with good absolute accuracy in different centers. We propose this standardization of quantities associated with analysis of dynamic contrast-enhanced MRI as part of building up a common language for the estimation and description of the physiologic quantities that determine the dynamic behavior of contrast agents.

We are specifically concerned with agents that are diffusable (ie, can pass out of the capillaries), and that remain extracellular (ie, are non-lipophilic) ie type 2 agents (50). Our goal in this is to clarify the parameters that can be useful in describing the uptake of Gd(III)-based contrast agents, because imaging this uptake has been shown to be clinically feasible and useful in predicting or measuring response to therapy in human tumors. Thus we exclude from the present discussion both very large molecules that remain intravascular, and also freely diffusable tracers such as labeled water and most gaseous tracers, which penetrate cells.

We gathered a group of authors who are experts in the basic science and/or clinical application of the MR tracer kinetic models. There has been a new surge of

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interest in the quantification and the assessment of efficacy and clinical utility due to the improvement of spatial and temporal resolution of the MR equipment. There is an urgent need to have a standardized nomenclature and quantification. Many publications, including those by the authors, report their results using different tracer kinetic models and terminology. With the rapid proliferation of research in this new and exciting field, a standardized nomenclature and quantification will facilitate understanding and development in this field.

With better quantification methodology and MR instrumentation, the estimation of each parameter is now approaching the "true" (absolute) values underlying the pathophysiologic processes that are being measured. Although we can continue to improve the calculations of the "true" values, they will ultimately be limited by the complexity of the underlying pathophysiology and the variations of techniques. However, even with very primitive methodologies and quantification, there is preliminary evidence that tracer kinetic modeling can be a potentially powerful tool in the management of cancer, stroke, and heart attack. That means that with continuing improvement of the tracer kinetic models, there will be significant improvement and expansion of its clinical utility. Therefore, a unified nomenclature and quantitation will be essential to facilitate these processes.

Here we propose a standard set of quantities, names, and symbols, with a view to achieving a global consensus on terminology. We have given alternative terms where these are in use. We show the relationship between these quantities and previously published work from our groups. We have moved to be consistent with long-standing work from the areas of flow measurement using non-NMR tracers (3–9) and pharmacokinetics (10,11) where possible, although these bodies of work contain some terminologic incompatibilities that cannot be resolved. We have aimed to be as model independent as we can (although many of the quantities have an implicit simple model of tissue behavior built into the definition of the quantity). In future publications we will adhere to these standardized terms (or their alternatives) in reporting our results, and where we use the alternatives, we will define them with respect to the standards.

STANDARDIZED QUANTITIES

We give proposals for standardized terms here (Table 1) a detailed discussion of the reasons for our choices is given in Appendix A.

Most methods of analyzing dynamic contrast-enhanced T_1-weighted data have used a compartmental analysis to obtain some combination of the three principle parameters: the transfer constant (K^{trans}), the extravascular extracellular space (EES) fractional volume (v_e), and the rate constant (k_{ep}). The transfer constant and the EES relate to the fundamental physiology, whereas the rate constant is the ratio of the transfer constant to the EES:

$$k_{ep} = K^{trans}/v_e. \quad (1)$$

The rate constant can be derived from the *shape* of the tracer concentration vs time data, whereas the transfer constant and EES require access to *absolute values* of tracer concentration.

The *transfer constant* K^{trans} has several physiologic interpretations, depending on the balance between capillary permeability and blood flow in the tissue of interest. In high-permeability situations (where flux across the endothelium is flow limited), the transfer constant is equal to the blood plasma flow per unit volume of tissue:

$$K^{trans} = F\rho(1 - Hct) \quad (PS \gg F) \quad (2)$$

(see Mixed Flow . . . section below; $F\rho$ and Hct are defined in Table 2). In the other limiting case of low permeability, where tracer flux is permeability limited, the transfer constant is equal to the permeability surface area product between blood plasma and the EES, per unit volume of tissue (2):

$$K^{trans} = PS\rho \quad (PS \ll F) \quad (3)$$

(see Mixed Flow . . . section below).

Tracer flows passively from the blood plasma in a permeable capillary into the EES, through microscopic pores or defects in the capillary walls. This has also been called the "interstitial water" or "interstitial space."

Table 1
Three Standard Kinetic Parameters (See Also Appendix A)

Symbol	Preferred short name	Units	Full name	Alternatives	Discontinued terms
K^{trans}	Transfer constant[a]	min^{-1}	Volume transfer constant between blood plasma and EES	EF, FE, CL_d/V_t[b]	k,$k^{PS\rho}$
k_{ep}	Rate constant	min^{-1}	Rate constant between EES and blood plasma	k_{21}, k_2, $1/\tau$[c]	
v_e	EES[d]	None	Volume of extravascular extracellular space per unit volume of tissue[e]	Interstitial space, leakage space	

[a]If permeability is high ($PS \gg F$, ie, Kety model), this is the blood plasma flow per unit volume of tissue ($K^{trans} \approx F\rho(1 - Hct)$). If permeability is low ($PS \ll F$), this is the permeability surface area product per unit volume of tissue, for transendothelial transport between plasma and EES ($K^{trans} \approx PS\rho$).
[b]EF is the extraction flow product; CL_d = clearance.
[c]k_{21}: see ref. 23; k_2 see refs. 17 and 22; $1/\tau$ see ref. 26.
[d]EES = extravascular extracellular space.
[e]ie, the volume fraction of the EES.

Table 2
Working Quantities (See Appendix A)

Quantity	Definition	Unit
C_a	Tracer concentration in arterial whole blood[a]	mM[b]
C_e	Tracer concentration in EES[c]	mM
C_p	Tracer concentration in arterial blood plasma[a]	mM
C_t	Tracer concentration in tissue	mM
C_v	Tracer concentration in venous whole blood	mM
CL_d	Distribution clearance[d]	ml min^{-1} [e]
E	Initial extraction ratio[f]	None
Hct	Hematocrit	None
F	Perfusion (or flow) of whole blood per unit mass of tissue	ml g^{-1} min^{-1}
P	Total permeability of capillary wall	cm min^{-1}
PS	Permeability surface area product per unit mass of tissue	ml min^{-1} g^{-1}
S	Surface area per unit mass of tissue	cm^2 g^{-1}
V_b	Total whole blood volume[g]	ml
V_e	Total EES volume[g]	ml
V_p	Total blood plasma volume[g]	ml
V_t	Total tissue volume[g]	ml
v_b	Whole blood volume per unit volume of tissue[g]	none
v_p	Blood plasma volume per unit volume of tissue[g]	none
λ	Tissue blood partition coefficient	ml g^{-1}
ρ	Density of tissue	g ml^{-1}

[a]$C_a = (1 - \text{Hct})C_p$.
[b]1 mM = 1 mmole/liter.
[c]EES = extravascular extracellular space.
[d]See Modeling Tissue Uptake of a Diffusable Tracer Section in text.
[e]1 ml = 1 cm^3.
[f]See Mixed Flow . . . Extraction Ratio Section in text (mixed model); abbreviated to "extraction"; extraction fraction is an alternative name.
[g]NB $V_b = v_b V_t$; $V_e = v_e V_t$; $V_p = v_p V_t = (1 - \text{Hct})V_b$.

Note that "extravascular" is included in the term, to exclude specifically the blood plasma space (which is technically part of the whole extracellular space).

The *rate constant* k_{ep} is formally the flux rate constant between the EES and blood plasma (2). Both the transfer constant and the rate constant have the same units (min^{-1}) and can easily be confused. The rate constant k_{ep} is always greater than the transfer constant K^{trans}. For a range of typical EES fractional volumes seen in tumors and multiple sclerosis (v_e = 20%–50%), k_{ep} is two to five times higher than K^{trans} (see Eq. [1]).

Other working quantities are shown in Table 2, and MRI quantities in Table 3. We suggest that these be used whenever possible to describe models and to report results, in order to facilitate communication and simplify the problem of comparing work between groups.

MODELING TISSUE UPTAKE OF A DIFFUSABLE TRACER

We summarize the principal approaches to physiologic and pharmacokinetic modeling that have been used, in enough detail to support the tables of parameters. More details, including the MRI aspects, are summarized elsewhere (2,9,12–15). We start with the simple, stereotypical cases of endothelial tracer flux being limited purely by flow or purely by permeability, before considering the more complex case of being limited by both flow and permeability. All the models we consider are simple two-compartment ones (ie, blood plasma and EES); they ignore both the contribution of intravascular tracer to the total tissue concentration and the possibility of further compartmentation within the voxel. However, they do enable common ground between diverse approaches to be identified.

Flow-Limited (Kety) Model (High Permeability)

Kety (3,9,13) produced a model of flow-limited tracer uptake in tissue that has been used extensively. It was developed for the case of breathing an inert gas, which distributes into the whole tissue, including the intracellular spaces. Its first assumption is that arterial and venous blood have well-defined concentrations, supplying and draining the tissue under study. Second, because permeability is high, venous blood leaves the tissue with a tracer concentration that is at all times in equilibrium with the tissue. Thus, soon after injection of the tracer, the arterial concentration is high, the venous concentration is low, and most of the tracer is being removed from the blood as it passes through the tissue. For an extracellular tracer, the Kety model can be extended by setting the venous concentration equal to that of the EES. The effect of intravascular tracer on the MR signal is ignored (ie, the vascular signal is small compared with the tissue signal). In this case the following differential equation relating tissue concentration C_t to arterial plasma concentration C_p is obtained (see Appendix B, Flow-Limited Kety model):

$$\frac{dC_t}{dt} = F\rho(1 - \text{Hct})\,(C_p - C_t/v_e). \qquad (4)$$

Note that the other quantities in this equation (F, ρ, H, and v_e) are constants for the tissue (Tables 1 and 2).

PS-Limited Model (Low Permeability)

If flow is high, the blood plasma can be considered as a single pool, with equal arterial and venous concentrations. The transport of tracer out of the vasculature is slow enough not to deplete the intravascular concentration. The rate of uptake is then determined by the permeability surface area product of the capillary wall and the difference between the blood plasma concentra-

Table 3
MRI Quantities

Quantity	Definition	Unit
R_1	Relaxation rate (≡1/T_1)	sec^{-1}
R_{10}	Native relaxation rate (≡1/T_{10})	sec^{-1}
r_1	T_1 relaxivity[a]	sec^{-1} mM^{-1}
T_{10}	Native T_1[b]	sec
ΔR_1	Change in relaxation rate caused by tracer[a]	sec^{-1}

[a]The realaxtivity is the increase in relaxation rate per unit concentration of tracer; thus $\Delta R_1 = r_1 C_t$; $R_1 = R_{10} + \Delta R_1 = R_{10} + r_1 C_t$ (assuming all the tracer is in fast exchange with the tissue water).
[b]The native T_1 is the T_1 of tissue before injection of Gd tracer.

tion and the EES concentration. If the contribution of tracer in the intravascular space is ignored, the transport equation is then (2,16) (see Appendix B, Permeability-Limited model):

$$\frac{dC_t}{dt} = PS\rho(C_p - C_t/v_e) \quad (5)$$

Mixed Flow- and PS-Limited Model: Extraction Ratio

Tracer uptake may be limited by both blood flow and permeability. The extraction ratio E (11) was first defined by Renkin (4); it is the fractional reduction in capillary blood concentration as it passes through tissue [$E = (C_a - C_v)/C_a$]. The initial extraction, when there is no backflow from EES to blood plasma, is a constant that characterizes a particular tissue and tracer combination. However, as the tissue concentration builds up after injection, backflow increases, and the extraction ratio decreases (4,17). Larsson et al (17) have called this E(t). In fact E(t) becomes negative when there is a net tracer flow back into the blood. Although the E(t) is thus not a constant for a particular tissue and tracer, the *initial extraction* E is an appropriate index that does characterize the tissue. The transport equation is (see Appendix B, Mixed Flow . . . section):

$$\frac{dC_t}{dt} = EF\rho(1 - \text{Hct})(C_p - C_t/v_e). \quad (6)$$

Kety (in ref. 3, p. 19) modeled the absorption of an inert gas from alveoli into capillaries; Renkin (4) clarified leakage of a blood-borne tracer into the interstitium. Modifying his approach to take account of the tracer being extracellular (Appendix B, Mixed Flow . . . Section), we find that the initial extraction ratio is $E = 1 - \exp[-PS/F(1 - \text{Hct})]$ (see Eq. [21]). Previous workers have omitted the $(1 - \text{Hct})$ factor, which is required because F is the flow of *whole* blood. Thus, in the flow-limited case ($PS \gg F$), the extraction is complete ($E = 1$) and the transport equation reduces to the Kety equation (Eq. [4]). In the PS-limited case ($PS \ll F$), $E = PS/F(1 - \text{Hct})$, and the equation reduces to Eq. [5].

St. Lawrence and Lee (13) have made a more complete analysis using a distributed parameter model, based on the approach of the Johnson and Wilson model (18); this includes capillary flow, permeability, and transit time. C_a and C_t must both be measured with sufficient temporal resolution (about 2 seconds) to detect tracer entering and passing through the capillary bed. (Thus intravascular tracer has to be completely visible). The four independent parameters $F\rho$, v_b, E, and v_e can then all be estimated (with E uncoupled from $F\rho$), and hence $PS\rho$ becomes available.

Clearance Model

Clearance (CL) is defined in pharmacokinetics as the constant of proportionality that relates the rate of elimination of a drug from a compartment to the current drug concentration (11). The clearance can be understood as the volume that is completely cleared of the drug in unit time. Distribution clearance CL_d can be defined in a similar way, for two connected compartments (see Appendix B, Clearance Model section); with the further assumption that intravascular tracer can be ignored, we obtain (Appendix B):

$$\frac{dC_t}{dt} = \frac{CL_d}{V_t}(C_p - C_t/v_e). \quad (7)$$

The clearance per unit volume of tissue CL_d/V_t and the EES v_e determine the pharmacokinetic behavior.

Generalized Kinetic Model

Equations [4–7] are all of the same form:

$$\frac{dC_t}{dt} = K^{trans}(C_p - C_t/v_e) = K^{trans}C_p - k_{ep}C_t. \quad (8)$$

Thus, for a variety of models (all of which ignore the contribution of intravascular tracer to tissue concentration), we expect tissue tracer to behave in the same way. This is behavior is determined by only the blood plasma concentration and two additional parameters, the transfer constant K^{trans} and the EES fractional volume v_e [or, alternatively, K^{trans} and the rate constant k_{ep} (= K^{trans}/v_e]. The transfer constant can be physically interpreted as follows. From Eqs. [4–7] we see that the transfer constant $K^{trans} = F\rho(1 - \text{Hct})$ under flow-limited conditions, $K^{trans} = PS\rho$ under PS-limited conditions, $K^{trans} = EF\rho(1 - \text{Hct})$ under mixed conditions, and in the drug clearance paradigm $K^{trans} = CL_d/V_t$. The general solution to Eq. [8] is given in Appendix B, Generalized Kinetic Model section, along with the response to bolus and step arterial inputs, and the residence time. We show that the rate constant k_{ep} is the exponential decay constant for tissue concentration that would result if the arterial concentration could be instantaneously raised from zero to a constant value, or dropped to zero (Eqs. [27 and 28]). It is also the mean residence time for tracer in the EES after a bolus arterial input.

MRI TECHNIQUES TO CHARACTERIZE TRANSCAPILLARY TRANSPORT OF CONTRAST AGENTS

A number of groups have characterized capillary leakage from MRI signal changes after injection of low molecular weight Gd(III) contrast agents. This work has been reviewed in detail elsewhere (2,9,13,15). It is difficult to compare the work of various investigators because the techniques vary in the injection procedure, in the MRI sequences and protocols, in the modeling of the MRI signal from a given tissue tracer concentration, whether pharmacokinetic modeling has been attempted, and the treatment given to intravascular tracer. However, we have shown that there are a limited number of fundamental parameters that characterize the tissue and that are MRI accessible. These are the three defined in Table 1 (ie, K^{trans}, v_e, k_{ep}) and possibly F, PS, and v_b (or v_p). In essence all the techniques can be judged by how

close they come to measuring these quantities accurately.

We now define how published estimates of parameters are related to the standard physiologic parameters used here. In London Tofts and Kermode (16), studying multiple sclerosis lesions, estimated the transfer constant K^{trans} (calling it k) and the EES (calling it leakage space v_1). Data from breast tumors were also analyzed (19). In a more recent review (2), Tofts called the transfer constant $k^{PS\rho}$. In Copenhagen Larsson and coworkers (20), also studying multiple sclerosis, estimated the rate constant k_{ep} (calling it EF/v). Measurements of transfer constant were also reported briefly (21). More recently, myocardial perfusion has been measured (17,22). In Heidelberg Brix and coworkers (23), studying a brain tumor, estimated the rate constant k_{ep} (calling it k_{21}) and a constant A, which is proportional to the transfer constant and other factors (2). Hoffman, Brix, Knopp, and coworkers, studying breast tumors (24), estimated the rate constant and a redefined constant A, which is proportional to the EES and other factors (2). k_{ep} was estimated for Gd-DTPA in malignant and benign mammary tumors by Port and coworkers (25); kinetic heterogeneity, ie, two or more different k_{ep} values acting in the same ROI, was discovered in most of the malignant tumors. In Nottingham, Gowland (26) studied brain tumors and estimated a time constant for transfer across the blood-brain barrier τ; from her transport equations we find $\tau = 1/k_{ep}$.

Shames and coworkers, in San Francisco, have employed a two-compartment tissue model (plasma and interstitial fluid) fitted to blood and tissue signal intensity to estimate PS and the fractional plasma volume in several rat tumors using Gd-DTPA and macromolecular Gd tracers (27,28). Hulka and coworkers, in Boston, estimated the extraction-flow product EF for Gd-DTPA in malignant and benign mammary tumors (29,30). Buckley and coworkers have measured pharmacokinetic parameters in the breast (31) and prostate (32). Henderson and coworkers measured $F\rho$, $PS\rho$, and v_b in canine mammary tumors using Gd-DTPA and gadomer-17 (33).

DISCUSSION AND CONCLUSIONS

We could not obtain complete agreement among all the authors of this paper on using a single set of terms for the quantities in Table 1; many of the terms have shortcomings, and different terms may be appropriate depending on the context of the study. Thus alternatives have been given. However, we did obtain agreement on the meanings of the terms, and their equivalences.

The measured transfer constant or rate constant is a potentially intractable combination of flow, permeability, and surface area. An independent estimate of flow (using spin tagging or bolus tracking) might give information on whether the tracer flux is flow limited or PS limited ($F \gg K^{trans}$ implies PS limited and $K^{trans} = PS\rho$; $F \ll K^{trans}$ implies flow limited and $K^{trans} = F\rho$). An independent estimate of blood volume (using bolus tracking) may give on information on whether S is changing. In the PS-limited case, for relatively small molecules such as gadopentetate dimeglumine, alterations in the transfer constant may reflect increases in capillary surface area rather than permeability.

Permeability is generally high for such small molecules, with the exception of hydrophilic molecules in healthy brain capillaries. The permeability to larger agents (such as Gd-DTPA albumin) is considerably lower, and these are probably better suited to detecting changes in the leakiness of the capillary endothelium. In tumors we are probably in the mixed flow- and PS-limited case; however, in the brain most cases are PS limited. We have assumed that the transfer constant between blood plasma and the EES is the same in both directions. There is no evidence of unequal transfer constants in the case of low molecular weight Gd(III) contrast agents; if required, equations to deal with this have been given (2).

The contribution of intravascular tracer to the MRI signal remains a problem for the modeling. Data collection is challenging if the first passage is to be temporally resolved. Neglecting it may be appropriate for a diffusable tracer, as Kety and others have done, since its distribution volume is large compared with the blood volume (34) (ie, we have assumed $v_b \ll 1$); however, the approximation is less appropriate for an extracellular tracer, where the distribution volume is smaller (ie, we are assuming $v_p \ll v_e$). Intravascular tracer could then contribute a large proportion of the observed tissue signal and give significant errors in estimates of K^{trans} if not accounted for in the modeling. In other imaging modalities [eg, x-ray CT (34,45)], an accurate modeling is possible, since all tracer in a voxel contributes to the signal, and moving tracer has the same effect as stationary tracer.

However, in MRI, intravascular tracer is likely to be in slow or intermediate exchange with tissue water (35,36), making it partially invisible to the tissue water. This reduces its influence on the T_1 of tissue water, depending on the particular T_1-weighted sequence that is used (35). At this point, proton exchange rates in tissues other than the myocardium, particularly in pathologies, are unknown, and so the degree to which tracer in the intravascular space will affect the contrast enhancement behavior is also unknown. Tumors and vascular organs such as the liver and the kidney often have high capillary permeability; this may be enough to make the intravascular tracer completely visible and more easily modeled for the flow-limited (Kety) situation. In contrast, high intravascular concentrations of tracer can dephase signal in the vessel and surrounding tissue, making it safe to neglect. The generalized kinetic model (Eq. [8]) refers to total tissue tracer. In the presence of intravascular tracer this equation should be recast to define the transfer and rate constants explicitly in terms of plasma and EES tracer:

$$v_e dC_e/dt = K^{trans}(C_p - C_e);\ dC_e/dt = k_{ep}(C_p - C_e).$$

The contribution of intravascular tracer can then be added to form $C = v_p C_p + v_e C_e$ if this is appropriate

(2,17,29,30), or a more complex model such as that described by St. Lawrence and Lee (13) may be used.

Several potential pitfalls in understanding the modeling literature have been identified here (mostly in Appendix A). These include confusion between quantities measured per mass and per volume of tissue (this may include assuming the density of tissue $\rho = 1$ g ml^{-1}), confusion between whole blood and blood plasma concentrations, and confusion between physiologic and pharmacokinetic concepts of extraction. In addition, the extraction ratio expression of Renkin (4) is inappropriate for an extracellular tracer and has been reformulated to include a hematocrit factor (Mixed Flow section, above, and Eq. [21]).

Heuristic enhancement parameters (such as the rate of enhancement, the time to peak, and the peak enhancement) may have some relation to physiologic parameters (2) although they also depend on the particular MRI sequence parameters (TR etc.). Among these, the dynamic enhancement pattern using the first-pass method with a bolus injection and T_1-weighted fast spin echo imaging have been extensively studied by Mayr et al (37–39). This method is easy to implement clinically with a scanning time of only 5 minutes and provides the following parameters: relative signal intensity (RSI) averaged over the plateau phase of the dynamic enhancement curve, and incremental rate of enhancement (representing the slope of the dynamic enhancement curve). Equilibrium distribution of contrast agent between tissue and blood pool may not play as an important a role in the first-pass method because the parameters are obtained during the early part of the dynamic contrast study. It is thought that the signal intensity observed early during the first pass (the slope) represents predominantly the concentration of contrast agent in the intravascular space, while the peak of the time intensity curve reflects the concentration of contrast agent in both the intravascular and extravascular interstitial space (40,41). Although parameters derived from the first-pass method remain semi-quantitative and do not allow for pharmacokinetic modeling, a significant correlation of these parameters and treatment outcome of cancer patients has been established (37–39).

Nonetheless the dependence of such empiric parameters on experimental and physiologic variables is not completely understood, and their lack of clear physiologic significance can make their interpretation difficult. In contrast, estimates of transfer constant, rate constant, and EES are, in principle, independent of the particular MR imager, sequence, and dose procedure used to make the measurements. In practice there will be some variations, depending on how good the methodology is. For example, insufficient temporal sampling of tissue and blood concentrations can have a large effect on the accuracy and precision of parameter estimates (42). However, the existence of globally agreed standard quantities will encourage research to improve the methodology with the aim of producing absolutely accurate measurements. It will also greatly simplify comparison of results from different groups. In the future we anticipate that absolute measurements of the standard physiological parameters defined here will be available and will form the basis of multi-center intercomparisons and trials (43).

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APPENDIX A: REASONING BEHIND CHOICE OF PARAMETER NAMES AND SYMBOLS

We now consider the parameters in Tables 1–3, giving detailed comments on our choice of symbols, terms, and units. We have tried to use parameters that follow on from previous work, that can be clearly distinguished from each other, and that will not lead to typographical ambiguities.

Three Standard Kinetic Parameters (Table 1)

Transfer Constant

This term was first used by Patlak (6) and has since been used by various groups employing other imaging modalities (12,44,45). We have formally called K^{trans} the "*volume* transfer constant" to distinguish it from a constant used by earlier workers, which refers to flux per unit *mass.* The symbol K_i was generally used, since it referred to influx (efflux, or backflow, was often ignored, to simplify the computations). We here use upper case and the superscript to distinguish it from the rate constant (see, eg, ref. 45), both when written and spoken. We retain the subscript to refer to the compartments between which tracer is flowing (eg, k_{ep}). We use "trans" rather than "t" to distinguish it from "tissue." In previous MRI work this parameter has been referred to as k (16) and $k^{PS\rho}$ (2). Larsson and co-workers have measured the unidirectional influx constant K_i (17,22,46), which is related by $K_i\rho(1 - \text{Hct}) = K^{trans}$, a volume of distribution $\lambda = v_e/\rho$, and a parameter $k_2 = k_{ep}$. The transfer constant has also been called "EF" or the extraction-flow product (see below). Some of us prefer not to use this term since we feel that K^{trans} is more general, and since EF can be confused with cardiac ejection fraction or MRI enhancement factor. The concept of extraction has to be carefully defined, since it has been used differently in the physiologic and pharmacokinetic literature (see below).

EES v_e

The term "extravascular extracellular space" (2,45) refers to the space into which tracer can leak from a capillary and has the benefit of specifically excluding the vascular space. "Interstitial space" (or "interstium") has been used for a long time. However, V_e has been used for many years, by Patlak and others (6,7) to denote the volume of this space, and to use a subscript "i" (for "interstium") risks confusion with "i" denoting intracellular space. There may be regions (such as fibrous tissue) that are in the EES yet are inaccessible to tracer. Alternatives would be "leakage space" (16) or

"distribution space." These latter are more technically correct, although they are less well understood by the radiologic and clinical community. We have therefore compromised on using v_e to denote the volume of the EES per unit volume of tissue. It is, strictly speaking, a "volume fraction" rather than a volume; it has no units, although expressing it as a percentage may be helpful.

Rate Constant k_{ep}

Yeung (45) called this the "rate constant of backflux from the EES to the plasma." We have used lower case and the subscript to avoid confusion with K^{trans}. In the Kety approach $k_{21} = EF/\lambda$ (using $K^{trans} = EF\rho(1 - Hct)$ and v_e from Eq. [14]). Since it is the ratio of two physiologically more fundamental parameters, there is a case for dispensing with k_{ep} and calling it K^{trans}/v_e.

Working Parameters (Table 2)

Tracer concentrations C_a, C_e, C_p, C_t, C_v are all expressed as volume concentrations (mM = mmole liter^{-1}), not mass concentrations (eg, mmole/100 g) as some previous workers have used. The alteration in T_1 is then simply related to these volume concentrations (Table 3). We have used whole blood tracer concentrations (C_a, C_v) and blood plasma concentration (C_p). Some workers (6) have used C_a to denote the concentration in the arterial blood plasma, which has the advantage of avoiding the (1 − Hct) term (Hct is the hematocrit; see Table 2), and thus simplifying some expressions. However, flow F is generally measured for whole blood (not plasma), and arterial concentrations determined using MRI are for whole blood, not blood plasma. The subscripts are in lower case, according to widespread previous use (3,6), although some pharmacokinetic work has used upper case (11). Some workers have used C_b for the mass concentration in brain tissue ($C_t = \rho C_b$); its use is discouraged since it could be confused with the concentration in the blood. The concentrations are all functions of time, and can be written $C_a(t)$, etc.

The extraction ratio E (4,11) has also been called "extraction *fraction*" (17,28); however, this can lead to confusion with "EF." Although its physiologic definition (as used in Appendix B, Mixed Flow . . . section) refers to the first pass, in pharmacokinetics it is defined as $(C_a - C_v)/C_v$ at any time after injection, and thus decreases with time (see Mixed Flow . . . section above).

We have retained the convention of F and S being specified per gram, to follow widespread physiologic and MRI practice. (This arose because the quantity of tissue could most easily be measured by weighing it.) Consequently the density ρ appears in most equations involving these quantities; the flow and PS per volume are $F\rho$ and $PS\rho$, respectively. Note that Kety (3) used F to denote *total* flow of blood (ml min^{-1}); some workers have used F to denote plasma flow per unit volume of tissue (this is $F\rho(1 - Hct)$ in our nomenclature). Absolute volumes (V_e, etc.) are denoted by upper case and fractional volumes (v_e, etc.) by lower case. The hematocrit Hct is the volume fraction of whole blood taken up by cells. We have already used this term (17). Thus the plasma fraction is 1 − Hct. In major vessels Hct ≈ 0.45; however, in small vessels it can be as low as 0.21 (34). The partition coefficient λ has units of ml g^{-1}, because Kety expressed tissue concentration per mass of tissue (see Appendix B, Flow-Limited . . . section). Larsson et al (17,22) used a quantity λ (= v_e/ρ), which differs from this by a factor (1 − Hct) (see Eq. [14]).

Note that k_{ep}, K^{trans}, v_e, etc. are *intensive* quantities, which are independent of voxel size (in homogenous tissue), and are suitable for MRI mapping. In contrast, CL_d, V_e, are *extensive* quantities, which increase with the amount of tissue being considered, and cannot meaningfully be mapped with MRI. Intensive quantities that are per unit mass (such as F) cannot be mapped with MRI, unless the density ρ is known (or assumed).

APPENDIX B: MODEL DETAILS

Flow-Limited Kety Model (3) (High Permeability)

The rate of tracer uptake in tissue per unit volume of tissue is the difference between arterial influx and venous efflux:

$$\frac{dC_t}{dt} = F\rho(C_a - C_v). \quad (9)$$

(The tissue density ρ is required because flow F is per unit gram of tissue.) Tissue and venous whole blood are assumed to always be in equilibrium (since permeability is high); the ratio of mass tissue concentration (C_t/ρ) to arterial whole blood concentration is the partition coefficient λ:

$$\frac{C_t}{\rho} = \lambda C_v. \quad (10)$$

We have used the mass tissue concentration (C_t/ρ), instead of volume tissue concentration (C_t) for consistency with the original treatment of Kety. Then

$$\frac{dC_t}{dt} = -\frac{F}{\lambda}(C_t - \lambda\rho C_a). \quad (11)$$

The original equation published by Kety (3) looks slightly different because mass tissue concentration (C_t/ρ) was used instead of volume concentration (C_t), and because he used total blood flow, not flow per unit mass of tissue. Since venous plasma and tissue EES are in equilibrium, we can derive λ in terms of v_e as follows. Ignoring the contribution of intravascular tracer to the tissue concentration (which in any case is unknown since $C_a \neq C_v$):

$$C_t = v_e C_e. \quad (12)$$

The venous plasma concentration $C_v/(1 - Hct)$ equals that in the EES (C_e), ie,

$$C_v = (1 - Hct)C_e \quad (13)$$

and using Eq. [10], we have

$$\lambda = \frac{v_e}{\rho(1 - \text{Hct})}. \quad (14)$$

Using $C_a = (1 - \text{Hct})C_p$, the Kety equation (Eq. [11]) then becomes:

$$\frac{dC_t}{dt} = F\rho(1 - \text{Hct})\,(C_p - C_t/v_e). \quad (15)$$

Permeability-Limited Model (High Flow)

Tracer flow into the EES in unit volume of tissue is (16)

$$v_e \frac{dC_e}{dt} = PS\rho(C_p - C_e). \quad (16)$$

We have assumed that permeability is the same for flux into and out of the EES. Again ignoring intravascular tracer,

$$C_t = v_e C_e$$

and

$$\frac{dC_t}{dt} = PS\rho(C_p - C_t/v_e). \quad (17)$$

Mixed Flow- and Permeability-Limited Model: Extraction Ratio

Following the approach of Kety (3), we assume tracer flux into the EES is proportional to the difference between plasma and EES concentrations:

$$\frac{dC_t}{dt} = \alpha(C_p - C_e) \quad (18)$$

where α is a constant to be determined. Initially we can ignore backflow ($C_e = 0$); using Eq. [9], we have $F\rho(C_a - C_v) = \alpha C_p = \alpha C_a/(1 - \text{Hct})$. The initial extraction $E = (C_a - C_v)/C_a$; hence $\alpha = EF\rho(1 - \text{Hct})$. Ignoring intravascular tracer, $C_e = C_t/v_e$ and

$$\frac{dC_t}{dt} = EF\rho(1 - \text{Hct})\,(C_p - C_t/v_e). \quad (19)$$

The original derivation of extraction ratio by Renkin was for a freely diffusable tracer (radioactive K^{43}), which can pass into blood cells (see ref. 4, p. 1208). His equation relating flow and diffusion in a single capillary must be modified for an extracellular tracer:

$$Q\,C_a(x) = P\,2\pi r\,\Delta x\,C_p(x) + Q\,C_a\,(x + \Delta x) \quad (20)$$

where Q is the blood flow into a single capillary of radius r and length l, as it passes through a slab of tissue between x and $x + \Delta x$. Setting $C_p = C_a/(1 - \text{Hct})$, and following his treatment, we find $C_a(l) = C_a(0)$ exp $[-P.2\pi rl/Q(1 - \text{Hct})]$, $P.2\pi rl/Q = PS/F$, and

$$E = 1 - e^{-PS/F(1-\text{Hct})}. \quad (21)$$

Since leakage of an extracellular tracer is from blood *plasma,* it is appropriate that the arterial blood plasma flow $F(1 - \text{Hct})$ should be in the expression.

Clearance Model

The distribution clearance, CL_d, (47) between two compartments A and B may be thought of as that volume that, along with its drug content, is transferred from compartment A to compartment B per unit time, while an equal volume, carrying the drug concentration of compartment B, is transferred from compartment B to compartment A. With the further assumption that intravascular tracer can be ignored, we obtain:

$$\frac{dA_t}{dt} = CL_d C_p - CL_d C_e \quad (22)$$

where A_t is the amount of drug in the tissue. Clearance is related to our previous work (23) using the constants k_{12} and k_{21} as follows: $CL_d = V_p k_{12} = V_e k_{21}$. Ignoring intravascular tracer, $C_e = C_t/v_e$. Since $A_t = C_t\,V_t$, we have:

$$\frac{dC_t}{dt} = \frac{CL_d}{V_t}(C_p - C_t/v_e). \quad (23)$$

Generalized Kinetic Model

The solution to Eq. [8], with the initial conditions that $C_p = C_t = 0$ at $t = 0$, is

$$C_t(t) = K^{\text{trans}} \int C_p\,(\tau)\,e^{-k_{ep}(t-\tau)}\,d\tau. \quad (24)$$

(45,48,49). The tissue response to a short arterial pulse of concentration = 1/(pulse duration), ie, a delta function, is

$$h(t) = K^{\text{trans}}\,e^{-k_{ep}t}. \quad (25)$$

Thus K^{trans} determines the amplitude of the initial response (the amount of tracer that enters the EES), and k_{ep} determines the washout rate from the EES back into the blood plasma (controlling the time for the impulse to die away). The mean residence time (26) is then:

$$\tau = \int_0^\infty t\,h(t)\,dt \Big/ \int_0^\infty h(t)\,dt = 1/k_{ep}. \quad (26)$$

The response to a step change in arterial plasma concentration, from 0 to C_{p0}, at time $t = 0$, is

$$C_t(t) = \frac{K^{\text{trans}}C_{p0}}{k_{ep}}(1 - e^{-k_{ep}t}) = v_e\,C_{p0}(1 - e^{-k_{ep}t}). \quad (27)$$

The response to a step change from C_{p0} to zero is

$$C_t(t) = \frac{K^{trans}\, C_{p0}}{k_{ep}}\, e^{-k_{ep}t} = v_e C_{p0} e^{-k_{ep}t}. \qquad (28)$$

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