Synopsis

Dynamic-contrast-enhanced MRI (DCE-MRI) has been widely used to characterize microvasculature permeability. Recently, it was shown to reveal metabolic activity using the shutter-speed pharmacokinetic paradigm (SSP), in which steady-state intra/extracellular water exchange kinetics was incorporated into DCE-MRI data analysis. Interesting insights into DCE-MRI signals come from modeling the extravascular tissue MR signal. The questions addressed here are, “When can extravascular $^1$H2O longitudinal magnetization recovery from inversion/saturation still be described by a single-exponential process, and when can the intra/extracellular water exchange kinetics be accurately determined?”

Purpose

Dynamic-contrast-enhanced MRI (DCE-MRI) is a widely used clinical imaging tool. A quantitative DCE-MRI protocol is a pharmacokinetic study. A paramagnetic contrast agent (CA) is injected intravenously and transiently extravasates only to the extravascular tissue spaces, a process described by Kety-Schmitt (KS) pharmacokinetic law (Figure 1). Interesting aspects of the analysis of DCE-MRI signals come from modeling the extravascular tissue MR signal. Typically, a tracer pharmacokinetic paradigm (TP) has been used, where longitudinal magnetization, $M$, recovery from inversion/saturation is assumed to be described by an empirical single exponential process with apparent relaxation rate, $\alpha$. However, this ignores an important feature of water compartmentalization, i.e., finite steady-state exchange of intra- and extracellular water molecules. In 1999, two-site-exchange (2SX) expressions for steady-state intra/extracellular water exchange kinetics (Figure 1) were incorporated into DCE-MRI data analysis, via the shutter-speed pharmacokinetic paradigm (SSP). SSP-based analysis not only characterize microvasculature, like TP, but also reveal cellular metabolic activity. In SSP models, $M$ is described with a bi-exponential function, which could admit two MR signals with different apparent relaxation rate constants. The questions addressed here are the conditions when $M$ relaxation can still be described as a single-exponential process and when the intra/extracellular water kinetics can still be accurately determined under SSP.

Methods

To illustrate the effects of varying [CA] during DCE-MRI, simulations with the following 2SX parameters (Figure 1): $f = 0.80, R_{100} = 0.55$ s$^{-1}$, and $f_{10} = 3.94$ s$^{-1}$mM$^{-1}$. The values were varied from 0 to 3 s$^{-1}$, with 0.5 s$^{-1}$ steps, and the [CA] values were varied from 0 to 6 mM. The simulations were run at two different intrinsic intracellular $^1$H2O relaxation rate constants: $R_{1i} = 0.55$ and 2.00 s$^{-1}$. In all simulations, the small microvascular plasma (and blood) signal was ignored.

The 2SX model describes intra- and extracellular $M$ with an empirical bi-exponential function,

$$\frac{M_0 - M(t_1)}{M_0} = (1 - \cos \alpha) \left[ f_{sm}' e^{-R_{1sm}t_1} + (1 - f_{sm}') e^{-R_{1lar}t_1} \right]$$

where $M(t_1)$ is the magnetization at recovery time $t_1$, $M_0$, at equilibrium, the effective flip angle of the inversion/saturation pulse, and $R_{1sm}$ and $R_{1lar}$ are the small and large apparent relaxation rate constants, respectively, and $f_{sm}'$ is the apparent fractional intensity of the signal with $R_{1sm}$. The analytical expressions for Eq. (1) quantities given in terms of physical quantities are described in Figure 2.

Results

The analytical 2SX solutions for $f_{ls}$, $R_{1lm}$, and $R'_{1lm}$ as functions of $[CA_o]$ and $k_{io}$ are illustrated in Figure 3. Without any exchange, both $f_{ls}$ and $R_{1lm}$ are $[CA]$-independent (horizontal dashed lines). With exchange, both parameters are strongly dependent on $[CA_o]$ and $k_{io}$ values. For $R_{1i} - R_{1i0} = 0$ s$^{-1}$, $f_{ls}$ is equal to 1.0 at $[CA_o] = 0$ mM for any finite $k_{io}$ value. For $R_{1i} - R_{1i0} = 1.45$ s$^{-1}$, $f_{ls}$ approaches 1.0 at $[CA_o] = 0.37$ mM ($R_{1i} - R_{1i0} = 0$ s$^{-1}$) for any finite $k_{io}$ value. In both cases, the recovery time-course could be well approximated with the single-exponential expression Eq. (1) with $R'_{1i}$.

**Discussions**

Figure 3 illustrates important theoretical features of the 2SX model. The abscissa is a measure of the longitudinal shutter-speed ($k_1 \equiv |R_{1i} - R_{1i0}|$) for this system. For simulations at $R_{1i} - R_{1i0} = 0$ and 1.45 s$^{-1}$, $f_{ls}$ approaches 0 as $k_1$ approaches zero. This has been traditionally called the fast-exchange-limit (FXL). However, the FXL term comes from NMR in chemistry, where reactions can be accelerated or slowed, i.e., $k_{io}$ can be increased or decreased, respectively. Figure 3 makes clear the $f_{ls}$ vanishing is independent of the $k_{io}$ value at finite $k_{io}$. Thus, the FXL label is misleading. It is more descriptive to refer to the left ordinate as the vanishing-shutter-speed-limit (VSSL). This is important because the TP represents a special case of the SSP – in the limit of a short SS. It has been shown algebraically that as $k_1$ vanishes, $R'_{1lm}$ approaches the $f$-weighted $R_{1ls}$, $R_{1ls}$ average [\( \equiv R'_{1i} \)]. Any DCE-MRI model within the TP is the special VSSL case of the analogous shutter-speed model.  

In most practical situations, ($R_{1i} - R_{1i0}$) is small in tissue but > 0 and $[CA_o]_{max}$ rarely exceeds 2 mM. In these cases, $f_{ls}$ is very small, and its signal also likely suffers disproportionate transverse relaxation quenching ($R'_{2ls}$ > $R_{2lm}$). Thus, the component can reasonably be neglected. In this very common regime, the recovery is mono-exponential, but the relaxation rate constant is $R'_{1lm}$ (Figure 2), not $R'_{1i}$ defined in TP model

\[
R'_{1i} = r_{1ls}[CA_o] + R'_{1ls}(2)
\]

This can be called the vanishing shutter-speed regime [VSSR]. Measurements in blood suggests the VSSR extends to $[CA_o]$ past 20 mM; most likely due to transverse quenching.8 This is important because $k_{io}$ is only accessible in the VSSR but not the VSSL.

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**References**


