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A reference agent model for DCE MRI can be used to quantify the relative vascular permeability of two MRI contrast agents

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ABSTRACT

Dynamic Contrast Enhancement (DCE) MRI has been used to measure the kinetic transport constant, K^{trans}, which is used to assess tumor angiogenesis and the effects of anti-angiogenic therapies. Standard DCE MRI methods must measure the pharmacokinetics of a contrast agent in the blood stream, known as the Arterial Input Function (AIF), which is then used as a reference for the pharmacokinetics of the agent in tumor tissue. However, the AIF is difficult to measure in pre-clinical tumor models and in patients. Moreover the AIF is dependent on the Fahraeus effect that causes a highly variable hematocrit (*Hct*) in tumor microvasculature, leading to erroneous estimates of K^{trans}. To overcome these problems, we have developed the Reference Agent Model (RAM) for DCE MRI analyses, which determines the relative K^{trans} of two contrast agents that are simultaneously co-injected and detected in the same tissue during a single DCE-MRI session. The RAM obviates the need to monitor the AIF because one contrast agent effectively serves as an internal reference in the tumor tissue for the other agent, and it also eliminates the systematic errors in the estimated K^{trans} caused by assuming an erroneous *Hct*. Simulations demonstrated that the RAM can accurately and precisely estimate the relative K^{trans} (R^{Ktrans}) of two agents. To experimentally evaluate the utility of RAM for analyzing DCE MRI results, we optimized a previously reported multiecho ^{19}F MRI method to detect two perfluorinated contrast agents that were co-injected during a single in vivo study and selectively detected in the same tumor location. The results demonstrated that RAM determined R^{Ktrans} with excellent accuracy and precision.

1. Introduction

Angiogenesis is critical for the sustained growth and metastasis of solid tumors, which negatively affects patient outcomes [1,2]. Anti-angiogenic therapies are often cytostatic (do not decrease tumor volume) thus evaluations of vascular permeability are often required to assess early therapeutic response [3]. Dynamic contrast enhanced MRI (DCE MRI) has been used to detect changes in vascular permeability, typically represented by the transfer constant K^{trans}, by monitoring the rate of uptake and/or washout of a MRI contrast agent (CA) in the tumor tissue [4]. The results from many DCE MRI studies have been correlated with microvessel densities [5], tumor grades [6], expression of VEGF [7], microarray gene expression analyses [8], tumor oxygenation [9], interstitial fluid pressure measurements [10], and biopsies [11].

Despite these promising results, DCE MRI has inherent limitations for quantitative pre-clinical and clinical cancer studies [12]. For example, the concentration of a CA in blood plasma must be monitored to provide an Arterial Input Function (AIF) that is required to determine K^{trans} using traditional DCE MRI analysis methods [13]. Identifying a suitable artery or vein within the MR image can be challenging, particularly for DCE MRI studies in mouse models of human cancers. Motion artifacts and in-flow effects also compromise the quality of the AIF. Furthermore, MR images must be acquired at a rate $\leq$ 5 sec per image to accurately estimate K^{trans} [14,15].

An often overlooked limitation of DCE MRI is the inability to account for the exact value of the hematocrit in the tumor microvasculature. Most DCE MRI studies assume that the arterial hematocrit is 40%, which is an acceptable estimate for patients with cancer [16]. Moreover, most studies assume that the hematocrit is a single value throughout the tumor and normal tissues. However, the

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hematocrit decreases as the vessel diameter decreases, so that the hematocrit in tumor microvasculature ranges between 20–80% of the hematocrit of a typical artery that is used for blood sampling [17]. This physiological condition is known as the Fahraeus effect [18]. The measured K^{trans} is linearly and inversely dependent on the hematocrit, therefore, overestimating the microvascular hematocrit directly translates to underestimating K^{trans} [19]. Similar effects of an erroneous hematocrit on the underestimation of K^{trans} have been reported, although these reports have been limited to the variability of large-vessel hematocrit between patients and have not addressed variability of capillary hematocrit in a single tumor [20,21]. A low hematocrit may contribute to hypoxia that can stimulate angiogenesis, increase vascular permeability and lead to high values of K^{trans}. Therefore, tumor regions with the highest K^{trans} may have the most underestimated K^{trans} values. This underestimation can be as great as 36%, which may partly explain why a 40% change in DCE MRI measurements is typically required to detect a statistically significant change in tumor angiogenesis in carefully controlled preclinical DCE MRI studies [22,23].

We propose a new model that addresses these limitations of DCE MRI. This new model, termed the Reference Agent Model (RAM), compares the pharmacokinetics of two CAs in the same tumor tissue, so that one agent may be used as a reference for the second agent. The RAM does not require measurement of the AIF. Because both CAs in the same tumor location must experience the same hematocrit, a ratiometric comparison of DCE MRI of both agents is independent of the hematocrit. More generally, a ratiometric approach has potential to cancel other characteristics of DCE MRI measurements that complicate the interpretation of the results. Therefore, this ratio of K^{trans}, known as R^{Ktrans}, should accurately represent the relative permeabilities of the two CAs. The derivation of RAM is presented in this report, along with computer simulations that evaluated the sensitivity of RAM to signal-to-noise ratio, temporal resolution, and extreme values of K^{trans} and the extracellular extravascular fractional volume (v_e).

To implement RAM, two MRI contrast agents must be selectively detected during a single DCE MRI scan session in the same tumor region for ROI analyses, or within each pixel within the image of the tumor for pixel-wise analyses. Because two co-injected T_1 and/or T_2 CAs are difficult to selectively detect with MRI, we have developed ^{19}F CAs and optimized ^{19}F MRI methods to perform simultaneous ^{19}F DCE MRI of two CAs in a mouse model of breast cancer. Our strategy is based on the ^{19}F MRI multi-echo approach developed by Girardeau, et al., for the highly sensitive detection of a single ^{19}F nanoemulsion in vivo [24,25]. However, instead of detecting a single ^{19}F CA, we investigated the co-injection of two different nanoemulsions and selective detection of each nanoemulsion in an interleaved fashion. The results of this ^{19}F DCE MRI study were analyzed using the RAM.

2. Theory

2.1. Derivation of the model

Our derivation of the RAM uses the notation and symbolic conventions described by Tofts et al. [26]. The RAM shares similarities with the Reference Region Model for DCE MRI, and therefore our derivation also uses the notation and symbolic conventions described by Yankeelov et al. [27]. The differential equations, Eqs. (1) and (2), describe the pharmacokinetic behavior of two contrast agents (CA) within a voxel. In this equation, $Cb_{CA\text{-}1}(t)$ and $Ct_{CA\text{-}1}(t)$ are the concentrations of one CA (CA-1) at time t in the blood and the tissue of interest respectively; $K^{trans,CA\text{-}1}$ is the transfer constant (min^{-1}) between the blood and the Extravascular Extracellular Space (EES) of the tissue of interest (TOI) for CA-1; v_e is the extravascular-extracellular fractional volume of TOI; and *Hct* is the hematocrit (fraction of blood volume occupied by red blood cells). A differential equation for the second contrast agent (CA-2) is analogous [Eq. (2)]. To emphasize the role of the hematocrit in this derivation, we have elected to include *Cb(t)* and *Hct* in these differential equations rather than use *Cp(t)*, which is a term that is more commonly used in derivations of DCE MRI theory. Yet *Cp(t)*, *Cb(t)*, and *Hct* are related through Eq. (3). For this derivation, we assumed that both agents are detected within the same TOI, thus v_e and *Hct* are the same for both agents.

$$\frac{dCt_{CA-1}(t)}{dt} = K^{trans,CA-1}\cdot\frac{Cb_{CA-1}(t)}{(1-Hct)} - \frac{K^{trans,CA-1}}{v_e}\cdot Ct_{CA-1}(t) \tag{1}$$

$$\frac{dCt_{CA-2}(t)}{dt} = K^{trans,CA-2}\cdot\frac{Cb_{CA-2}(t)}{(1-Hct)} - \frac{K^{trans,CA-2}}{v_e}\cdot Ct_{CA-2}(t) \tag{2}$$

$$Cp(t) = \frac{Cb(t)}{(1-Hct)} \tag{3}$$

The AIF can be eliminated from Eq. (1) by assuming that both agents show the same AIF, solving Eq. (2) for *Cb(t)/(1-Hct)* [Eq. (4)], and substituting Eq. (4) into Eq. (1), resulting in Eqs. (5a) and (5b).

$$\frac{Cb(t)}{(1-Hct)} = \frac{1}{K^{trans,CA-2}}\cdot\frac{dCt_{CA-2}(t)}{dt} + \frac{1}{v_e}\cdot Ct_{CA-2}(t) \tag{4}$$

$$\frac{dCt_{CA-1}(t)}{dt} = \frac{K^{trans,CA-1}}{K^{trans,CA-2}}\cdot\frac{dCt_{CA-2}(t)}{dt} + \frac{K^{trans,CA-1}}{v_e}\cdot Ct_{CA-2}(t) - \frac{K^{trans,CA-1}}{v_e}\cdot Ct_{CA-1}(t) \tag{5a}$$

$$\frac{dCt_{CA-1}(t)}{dt} = \frac{K^{trans,CA-1}}{K^{trans,CA-2}}\cdot\frac{dCt_{CA-2}(t)}{dt} + \frac{K^{trans,CA-1}}{v_e}\cdot[Ct_{CA-2}(t) - Ct_{CA-1}(t)] \tag{5b}$$

Integrating both sides of Eq. (5b) and assuming that the initial concentrations of CA-1 and CA-2 are equal to zero yields the working equation for the RAM [Eq. (6)] where R^{Ktrans} is the relative $K^{trans,CA\text{-}1}$ compared to $K^{trans,CA\text{-}2}$, and $k_{ep,CA\text{-}1}$ is the rate constant (min^{-1}) between the EES of the TOI and plasma for CA-1.

$$Ct_{CA-1}(T) = \frac{K^{trans,CA-1}}{K^{trans,CA-2}}\cdot Ct_{CA-2}(T) + \frac{K^{trans,CA-1}}{v_e}\cdot\left[\int_0^T Ct_{CA-2}(t)\,dt - \int_0^T Ct_{CA-1}(t)\,dt\right] \tag{6a}$$

$$Ct_{CA-1}(T) = R^{Ktrans}\cdot Ct_{CA-2}(T) + k_{ep,CA-1}\cdot\left[\int_0^T Ct_{CA-2}(t)\,dt - \int_0^T Ct_{CA-1}(t)\,dt\right] \tag{6b}$$

The RAM can be expressed in matrix form [Eqs. (7) and (8)]. The elements of column two of vector M in Eq. (8) can be approximated by numerical integration. Eq. (8) is a system of linear equations, which can be solved for the elements of vector b using linear algebra.

$$\vec{A} = \vec{M}\cdot\vec{b} \tag{7}$$