Physica Medica 34 (2017) 38–47

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Original paper

Assessment of micronecrotic tumor tissue using dynamic contrast-enhanced magnetic resonance imaging

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ARTICLE INFO

Article history:
Received 13 September 2016
Received in Revised form 22 December 2016
Accepted 14 January 2017
Available online 27 January 2017

Keywords:
DCE-MRI
Diffusion
Contrast agent
Interstitium
Tumor
Necrotic tissue

ABSTRACT

Compartmental models for evaluation of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) datasets assume a homogeneous interstitital volume distribution and homogeneous contrast agent (CA) distribution within each compartment, neglecting effects of CA diffusion within the compartments. When necrotic or micronecrotic tumor tissue is present, these assumptions may no longer be valid. Therefore, the present study investigates the validity of three compartmental models in assessing tumors with necrotic components.

The general diffusion equation for inhomogeneous tissue was used to simulate the extravasation of a low-molecular-weight contrast agent from a feeding vessel into the interstitial space. The simulated concentration-time curves were evaluated using the extended Tofts model, a parallel 3-compartment model, and a sequential 3-compartment model.

The extended Tofts model overestimated the interstitial volume fraction by a median of 6.9% resp. 10.0% and the parallel 3-compartment model by 8.6% resp. 15.5%, while the sequential 3-compartment model overestimated it by 0.2% resp. underestimated it by 18.8% when simulating a mean vessel distance of 100 μm resp. 150 μm. Overall, the sequential 3-compartment model provided more reliable results both for the total fractional interstitial volume and for the interstitial subcompartments.

1. Introduction

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) typically uses low-molecular-weight contrast agents (LMWCAs). These LMWCAs extravasate instantaniously into the interstitial space, also known as the extravascular extracellular space. To assess enhancement after contrast agent administration, several pharmacokinetic compartmental models are used [1,2]. The most popular pharmacokinetic compartmental model is the so-called Tofts model [3], which uses a transfer constant to assess contrast enhancement. All of these models assume a homogeneous tracer concentration within each compartment and do not take diffusion effects into account. Thus, the permeability surface product of the supporting vascular network obtained with use of compartmental model is far from reflecting the true value [4].

Another parameter assessed by DCE-MRI is the fractional interstitial volume. This is an important and widely used parameter because changes in the interstitial volume of a tissue can indicate pathology. Tumors, in particular, have a markedly altered interstitial volume compared with healthy tissue, and the interstitial volume can vary within a tumor. Angiogenesis in a tumor is irregular, resulting in inhomogeneous oxygen supply across the tumor with development of micronecrotic and hypoxic tissue in areas receiving less oxygen [5,6]. Typically, tissue oxygen supply decreases with the distance from blood vessels. Therefore, tissue near vessels receives enough oxygen, while tissue farther away becomes hypoxic and tissue even farther away undergoes necrosis [7,8]. Such a tumor thus varies in relative interstitial tissue volumes with necrotic components having a markedly higher interstitial volume and a slightly higher diffusion coefficient.

Hypoxic areas in a tumor lower its sensitivity to radiation, thus considerably limiting the benefit of radiotherapy [9–12]. This has been discussed as a possible reason for the still rather poor local control rate of advanced head and neck tumors even in patients treated with an optimal combination of radiotherapy and chemotherapy [13] [14]. For prostate cancer, it has been shown that dose escalation in hypoxic areas is beneficial [15].

While pharmacokinetic compartmental models fail to provide reliable values for the permeability surface product, they perform much better in quantifying the fractional interstitial volume. Tissue with late contrast enhancement is potentially necrotic or micronecrotic because it is so far away from the nearest vessel that the diffusion distance of oxygen is exceeded [16]. As a result, it

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http://dx.doi.org/10.1016/j.ejmp.2017.01.010
1120-1797/

takes very long for low-molecular-weight contrast agents to fill the interstitial space of necrotic tissue areas [17]. DCE-MRI thus allows identification of micronecrotic areas with increased interstitial volume [17] and long diffusion distances. Often compartment models provide realistic interstitial volume values, but sometimes authors calculated interstitial volumes larger than 100% [18]. Moreover, compartmental models sometimes also fail to provide true fractional interstitial volumes. This is especially a problem in case of slow uptake [18] by poorly perfused tissues. None of the currently available compartmental models takes an inhomogeneous interstitial volume into account. Therefore, their ability to assess the interstitial volume fraction in tumors with inhomogeneously perfused tissue remains unknown.

The aim of the present study is to assess how reliably different compartmental models determine interstitial volume fraction in the presence of an inhomogeneous interstitial volume distribution. Therefore, extravasation and distribution by diffusion of an LMWCA in the interstitial space were simulated. A simplified tissue model was designed consisting of a central area with a small interstitial volume and a peripheral area with a higher interstitial volume. Since the simulation parameters, e.g. fractional interstitial volume, were to be varied continuously, macroscopic tissue description was chosen [19]. Three models were evaluated, the extended Tofts model, a parallel 3-compartment model, and a sequential 3-compartment model. When a 3-compartment model is used, each tissue type is represented by one compartment.

2. Theory

2.1. Diffusion equation

Diffusion in the extracellular space of a homogeneous biological tissue can be excellently described by solving the macroscopic differential equation [4,19–21]. For a porous medium, this is done by making several assumptions, namely that diffusion coefficient D and porosity ε are the same throughout the medium, while a tortuosity parameter, λ, is used to account for effects of porosity on diffusion processes. The indicator concentration in the interstitial volume, $\langle C\rangle_e$, and thus the averaged diffusion equation for homogeneous porous media is given by the following equation [19]:

$$\varepsilon\frac{\partial\langle C\rangle_e}{\partial t}=\frac{\varepsilon D}{\lambda^2}\nabla^2\langle C\rangle_e \tag{1}$$

However, since biological tissues are often inhomogeneous, we need a diffusion equation that also applies to inhomogeneous tissues, which are characterized by the fact that parameters such as the diffusion coefficient or relative interstitial volume vary with the spatial position within the tissue. The general diffusion equation for porous media has the following form [22]:

$$\varepsilon\frac{\partial\langle C\rangle_e}{\partial t}=\nabla\cdot\left[\frac{\varepsilon D}{\lambda^2}\nabla\langle C\rangle_e\right] \tag{2}$$

Tortuosity λ accounts for restriction and deceleration of diffusion processes in biological tissues compared with free media. Tortuosity λ can be interpreted as a composite parameter accounting for both the longer geometric diffusion pathway around cells in the interstitial space and the effects of interstitial viscosity [23]:

$$\lambda=\lambda_g\lambda_v. \tag{3}$$

λ_g represents the geometric component of tortuosity and λ_v its viscous component. Viscosity slows down diffusion through the presence of macromolecules in the interstitial space, which can become obstacles for diffusing particles [21]. The geometric effect of longer diffusion pathways in the extracellular space results from the tortuosity of diffusion pathways around cells [24]. Low-molecular-weight indicators do not enter cells, instead taking the longer routes around them. Geometric tortuosity is defined as the ratio of the actual effective pathway, L_{eff}, between two points to the shortest distance, L, between the two points:

$$\lambda_g=\frac{L_{eff}}{L} \tag{4}$$

In an experimental setup for determining λ in a tissue of interest, one has to take both geometric effects and interstitial viscosity into account. This is accomplished by interpreting tortuosity in relation to diffusion coefficients D and D_{eff} [21]:

$$\lambda=\sqrt{\frac{D}{D_{eff}}} \tag{5}$$

Therefore, λ is determined by first measuring the diffusion coefficient, D, for a given molecule in free aqueous medium or gel and then comparing this value with the effective diffusion coefficient, D_{eff}, measured for the same molecule in the target tissue. If diffusion is slowed or restricted, for instance due to the presence of cells in biological tissue that cannot be penetrated by a contrast agent, then $\lambda>1$. Other factors that can affect diffusion in the extracellular space include entrapment in so-called dead spaces, binding, and uptake of diffusing particles into the tissue [24], which are not taken into account here.

2.2. Relationship between tortuosity and porosity

The relationship between the parameters of tortuosity, λ, and porosity, ε, is important for describing diffusion in a porous medium. Several studies, primarily in the brain, have been conducted to elucidate the relationship between these two parameters [23,25,26]. Tao and Nicholson [25], for example, performed Monte Carlo simulation of 3D diffusion. They constructed three different extracellular space geometries to investigate effects of tissue geometry and structural properties on tortuosity, λ. For each of the three models, they performed simulations with different extracellular space volumes, ε. They found tortuosity λ to be independent of extracellular space geometry and, for all three models investigated, can be described by the following equation:

$$\lambda=\sqrt{\frac{3-\varepsilon}{2}} \tag{6}$$

Mota et al. [23] analyzed published experimental diffusion data obtained in central nervous system tissue to derive a general relationship between λ and ε:

$$\lambda=\varepsilon^{-n}. \tag{7}$$

In this equation, n is the index of tortuosity and depends on porosity ε of the medium investigated. Most values of index n for experimental diffusion data are distributed in the range Mota et al. [23] defined by the upper threshold of $n=0.23+0.3\varepsilon+\varepsilon^2$ and the lower threshold of $n=0.23+\varepsilon^2$ for n. In the present study, we use the mean value for n:

$$n=0.23+0.15\varepsilon+\varepsilon^2. \tag{8}$$

Therefore, tortuosity can be calculated using the following equation, assuming that porosity is known:

$$\lambda=\varepsilon^{-(0.23+0.15\varepsilon+\varepsilon^2)}. \tag{9}$$

Fig. 1 represents Eqs. (6) and (9) as curves.

It follows from Eq. (6) that λ increases with decreasing ε and can have a maximum value of $\lambda=1.225$ (see Fig. 1). However, experimental determination of λ in other studies [20,24,27] yielded a tortuosity λ of approx. 1.6 for the typical $\varepsilon=0.2$ in the brain. The deviation of λ determined with Eq. (6) from this value might be