Limits of Accuracy in Assessing Vessel Permeabilities Using Permeability-Surface(PS)-Limited Two-Compartment Models

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Introduction

Compartment models are widely used to quantify extravasation of low-molecular-weight contrast media (CM) in dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) [1]. However, little systematic work has been done on the limitations of compartment models. The aim of this work is to assess systematically possible over- and underestimation of vascular permeability, using compartment models, compared to the actual microscopic CM distribution in tissue. To this end, numerical diffusion simulations for several tissue models, describing the CM distribution process at the microscopic scale, are compared with a standard PS-limited (low permeability) two-compartment model [1] .

Material and Methods

The numerical simulation of CM-diffusion was performed in two spatial dimensions with a finite difference forward in time centered in space (FTCS) scheme in a regular grid with spatial discretization of 1 μm and a field of view of 50 μm x 50 μm and 200 μm x 200 μm. Using the FTCS scheme the CM-concentration was calculated for each spatial grid point by solving the diffusion equation numerically. In the center of the simulated area a circular vessel 10 μm in diameter (in the 50 μm x 50 μm simulation) and 20 μm in diameter (in the 200 μm x 200 μm simulation) and a wall thickness of 1 μm was put. Periodic boundary conditions were used to simulate a tissue with an intercapillary distances of about 50 μm and 200 μm respectively. These intercapillary distances were chosen in accordance with histological data of a rat prostate tumor model.
The CM-concentration in the vessel was given by a typical arterial input function (AIF). Furthermore the diffusion coefficient in tissue outside the vessel was set to D=260 μm²/s [2]. Permeability of the vessel wall was varied and the spatial CM-distribution simulated over 800 seconds. In the next step, a two compartment model was fitted to the simulated concentration time evolution to determine the corresponding permeability. Ideally the vessel wall permeability chosen in the diffusion simulation should be reproduced by the two compartment model. This is achieved only if D is very high (since the diffusion time in compartment models is intrinsically infinite) and vessel wall permeability is low enough (since we used a PS-limited compartment model).

Results

It was found that the two-compartment model underestimates vessel wall permeability compared to the actual vessel wall permeability of the diffusion simulation. As expected, the larger D and the smaller the vessel wall permeability P in the diffusion simulation, the better the results of the two-compartment model (curves get closer to straight line in Fig.1). For the tumor model (Fig. 1 A) and vessel wall permeability in the diffusion simulation of P=5 μm/s, the two- compartment model yields P=4 μm/s, i.e. an underestimation error of 20%. This error decreases for smaller wall permeabilities: error of 17% for P=2 μm/s, 7% for P=1 μm/s and 3% for P=0.1 μm/s. For solutes like sodium fluorescein (with radius 0.45 nm comparable to a low molecular weight CM like Ga-DTPA) Fu et al. [3] measured a capillary permeability of 0.344 μm/s. This value seems to be small enough for an two compartment approach with an underestimation error between 3% and 7%. However Fu et al. measured the permeability for larger capillaries (20-30 μm in diameter) with probably thicker walls and therefore lower permeability than smaller vessels as simulated here. The same situation is found in the normal tissue model (Fig. 1 B), with the difference that for lower diffusion coefficients in tissue, like D=80 μm²/s, the underestimation of two compartment models is even larger. While for higher tissue diffusion coefficients like D=260 μm²/s the underestimation in tumor and normal tissue are almost the same.

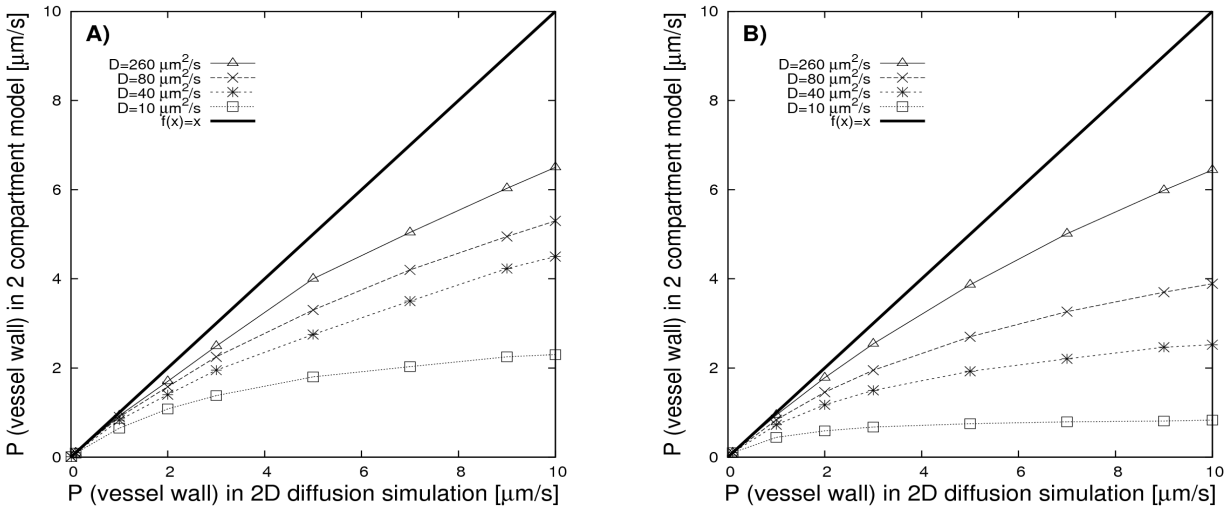

Fig. 1: Various simulations for different CM diffusion coefficients D in tissue. The thick line, f(x)=x, indicates the were the two-compartment model would predict the actual vessel wall permeability as chosen in the diffusion simulation.
A) Underestimation of vessel wall permeability values determined by two-compartment model for a mean capillary distance of 50 μm (tumor model). B) Underestimation of permeability values determined by two-compartment model for a mean capillary distance of 200 μm (normal tissue).

Conclusions

Determination of permeability using two-compartment models tends to underestimate the actual vessel wall permeability unless it is small enough. Therefore, the results of two-compartment models in combination with low molecular weight CM, as they are used in DCE-MRI to determine vascular permeability, remain dubious until they are confirmed by independent measurements of permeability.

[1] Tofts, PS et al. 1999, JMRI 10:233-232
[2] Gordon, MJ et al. 1999, Biotechnology and Bioengineering 65:459-467
[3] Fu, BM et al. 1998 Am J Physiol Heart Circ Physiol 274:2062-2073