About the Limitations of the PS-limited Tofts Model

G. Correia Carreira[1], D. Beyersdorff[2], and L. Luedemann[3]

[1]Radiology, Charite Medical School, Berlin, Germany, [2]Radiology, Bethel Hospital, Berlin, Germany, [3]Charite Medical School, Germany

Introduction

Compartment models are widely used to quantify physiological parameters such as capillary permeability, P, or extravascular extracellular fractional volume, v_e [1]. Usually the extravasation of low-molecular-weight contrast media (CM) in dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) lead to intensity time curves. To these the respective compartment models are fitted. Even though this is a standard procedure, little systematic work has been done on the limitations of compartment models. This work shows that compartment models may indicate a variation of P and v_e even when there is no such change in these tissue parameters, but in different ones, i.e. tissue tortuosity, λ, [2] and vessel distance. 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 Tofts model [1] .

Material and Methods

The numerical simulation of spatial CM-diffusion in tissue was performed with a spatial discretization of 1 µm and simulated areas of 50 µm x 50 µm up to 300 µm x 300 µm of extension. The CM-concentration in tissue, C, was calculated for each spatial grid point of the simulated area by solving the diffusion equation (Eq.(1)) in tissue [2] numerically.

$$\frac{\partial C}{\partial t} = \frac{D}{\lambda^2}\nabla^2 C + \frac{Q}{\alpha} \quad \text{Eq. (1)} \qquad \frac{dC}{dt} = PS\rho(C_p - \frac{C}{v_e}) \quad \text{Eq. (2)}$$

Tortuosity λ accounts for the impact of granular structure of tissue on the diffusion [2]. Tortuosity is defined as $\lambda = (D/D_{eff})^{0.5}$, where D is the diffusion coefficient in the extravascular extracellular space and D_{eff} the effective diffusion coefficient in the overall tissue (including cells and extravascular extracellular space). The tortuosity accounts for the changed diffusion path of the CM since it has to take longer ways around the cells which results in a lower effective diffusion coefficient. In the case where there are no cells at all λ =1. Q is a source term and α the extravascular extracellular fractional volume. Therefore the α in [2] corresponds to v_e in [1]. Typical pairs of values of tortuosity and α measured in brain are λ =1.6 and α=0.2 for normal brain tissue up to λ =2.3 and α=0.05 for ischemic tissue [2,3]. In the center of the simulated area a circular vessel 8 µm in diameter and a wall thickness of 1 µm was put. Periodic boundary conditions were used to simulate a tissue with an intercapillary distances of 50 µm up two 300 µm respectively. These intercapillary distances were chosen in accordance with histological data of a rat prostate tumor model [4] showing that tumors show significant smaller intercapillary distances than normal tissue. The CM-concentration in the vessel was given by an arterial input function (AIF). Furthermore the diffusion coefficient in tissue outside the vessel was set to D=260 µm²/s [5]. P was set to a literature value of 0.3 µm/s [6] as well as a higher and lower value of 3.3 µm/s and 0.03 µm/s. Tissue tortuosity λ was varied over a range of 1 to 2.3 and the corresponding spatial CM-distribution simulated over 600 seconds. In the next step, the PS-limited Tofts model (Eq. (2), where S is the vessel surface, ρ the tissue density and C_p the CM concentration in plasma) was fitted to the simulated concentration time evolution to determine the corresponding vessel permeability P and v_e.

Results

Ideally the chosen permeabilites and v_e from the diffusion simulation should be reproduced by the Tofts model. It was found that neither the capillary permeability nor v_e were predicted correctly by the Tofts model. Fitting the Tofts model to the simulated concentration time curves gave P and v_e, which are schown in Fig. 1. For varying tortuosities and vessel distances the Tofts model showed little variance in permeability. A higher actual permeability leads to a higher permeability predicted by the Tofts model (Fig. 1 A)). The found vessel permeabilities were always about half the actual value. The extravascular extracellular fractional volume v_e found by the Tofts model varies with tortuosity, permeability and vessel distance. It is particularly sensitive to the permeability. Changes in tortuosity have only a small effect on v_e in contrast to vessel distance. For normal (P=0.3 µm/s) and lower (P=0.03) permeability the Tofts model gives only unphysiological values of v_e larger than 1 (Fig. 1 B, note that the curves for P=0.03 are not shown in Fig 1 because the permeabilities are arround 0.013 µm/s and v_e=1.7 at vesseldistances of 30 µm going even steeper up than in the case of P=0.3 µm/s). For P=3.3 µm/s only in the case of λ =2.3 there are physiological meaningful values of v_e but they are still far away from α=0.04 which in cases of λ =2.3 is commonly measured [3].

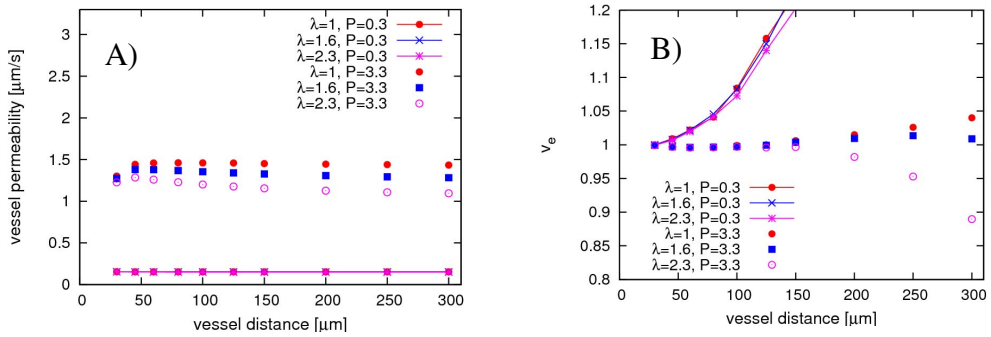

Fig. 1: Parameters found by fitting the Tofts model at the simulated concentration time curves. A) Underestimation of capillary permeability by the Tofts model for various tortuosities and vessel distances. B) Predicted extravascular extracellular fractional volume v_e by the Tofts model for various tortuosities and vessel distances.

Conclusions

Determination of capillary permeability by the Tofts model tends to underestimate the actual vessel permeability while v_e depends strongly on vessel distance, a property which is completely unconsidered in the Tofts model. Therefore changing v_e may indicate wrongly to extravascular extracellular fractional volume when in fact the vessel distance is varying and vice versa. Low vessel permeability can cause unphysiological values of v_e. The results of compartment models like the PS-limited Tofts model in determining vascular permeability remain problematic in their interpretation. Besides simulation based analysis like in this work, further independent physiological and phantom measurements of permeability and v_e are needed to clarify what compartment models are really telling us about the examined tissue.

References

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