Accuracy Evaluation of a First-Pass Pharmacokinetic Model (FPPM) for Simultaneous Mapping of Blood Volume and Microvascular Permeability in Brain Tumors

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Introduction

Simultaneous evaluation of cerebral blood volume and microvascular permeability constants is highly desirable in brain tumors [1]. This can be understood because the cerebral blood volume plays an important role in providing neovascular information to characterize the neoplastic process in tumors [2,3], whereas the microvascular permeability increases due to poor formations of endothelial cells and physiological effects of the angiogenic stimulator. A recently developed first-pass pharmacokinetic model (FPPM) demonstrated the feasibility of such simultaneous evaluation of blood volume and permeability on the basis of dynamic T2*-weighted images [1]. In this study, we aim to further investigate the estimation accuracy of the model parameters by using computer simulations.

Materials and Methods

The dynamic concentration-time curve for brain tissue following contrast administration, $C_t(t)$, can be represented by the equation based on the FPPM model proposed by Johnson et al.[1]:

$$C_t(t) = XS(t) + Y\int_0^t S(t')\exp(-k_{ep}(t-t'))dt' \; ; X = Av_p ; Y = AK^{trans} \quad . \qquad (1)$$

where v_p represents the fractional plasma volume; K^{trans} and k_{ep} are the transfer and the rate constants. S(t) is directly related to the plasma concentration function, $C_p(t)$, which in turn is associated with the arterial input and the recirculation. S(t) is thus modeled by taking into account the gamma variate bolus shape function, g(t), together with an integral term [1]:

$$C_p(t) = AS(t); \mathrm{S(t)} = \mathrm{g(t)} + \lambda\int_0^t \mathrm{g(t-t')}\,\mathrm{dt'}\,; \mathrm{g(t)} = \mathrm{(t-t')}^{\alpha}\exp(-\beta(\mathrm{t-t_0})) \quad \mathrm{t > t_0} \qquad (2)$$

Note that g(t) represents a gamma variate function with three unknown parameters (t_0 , α and β) and A is a scale factor. Combining Eqs.(1) and (2), there are hence 8 unknown parameters to be solved during the fitting process (k_{ep}, A, v_p,K^{trans} , λ , t_0 , α and β). Since multi-parametric curve fitting is known to be prone to inaccuracy from error accumulation, the following investigation on SNR effects was performed.

A contrast concentration curve of a patient with meningioma was first obtained, with all FPPM parameters calculated by means of a nonlinear least-square curve fitting method according to Eqs.(1) and (2). These parameters were treated as the true values to construct a model $C_t(t)$ curve. The same process was repeated for different regions within and outside regions such that $C_t(t)$ curves with various behaviors were included. White Gaussian noise was then added to the model curves to generate data sets with different SNR levels (SNR=5, 10, 15, 20, 30 and 40). 1000 trials of fitting process were performed with each set of data using the FPPM model and the percentage of estimation error was subsequently derived. The processing of each set of perfusion data took 2-5 hours using in-house programs written in MATLAB. In addition to error assessment via simulations, pixel-by-pixel fitting with the FPPM model was also tested on images from patients with brain tumors. All MR images were acquired at 1.5T (Magnetom Vision+; Siemens, Erlangen, Germany) with a series of 60-75 dynamic gradient-echo echo-planar images (TE=44ms, FOV=230×230 mm, matrix=128×128, flip angle=90°) at 1-second interval.

Results

The mean values and standard deviations of estimation errors for three physiological model parameters were shown in Fig.1. v_p and K^{trans} exhibited the expected increase in precision and accuracy as the SNR increased. However, estimation for K^{trans} showed poor precision, having errors as large as 150% even at the SNR of 20. k_{ep} showed an unexpected behavior of decreasing accuracy as SNR increased (arrow in Fig.1), despite good precision level. v_p showed the least fitting failures and high reproducibility with the lowest variation as compared to those of K^{trans} and k_{ep}. The parametric maps obtained using FPPM model were illustrated in Figs.2B-2D along with a relative cerebral blood volume (rCBV) map (Fig.2A) derived using conventional tracer kinetic model. The parametric image of v_p had much lower levels of noise while the K^{trans} and especially k_{ep} maps are far noisier, in agreement with the prediction from simulation results. There is close concordance between v_p map in Fig.2B and the rCBV map in Fig.2A, except that the former is free from the problem of overestimation from slow wash-out due to vessel tortuosity or second-pass transit (open arrows in Fig.2), plus that an absolute quantification of rCBV is possible using the FPPM model from a multiplication of v_p by the voxel size.

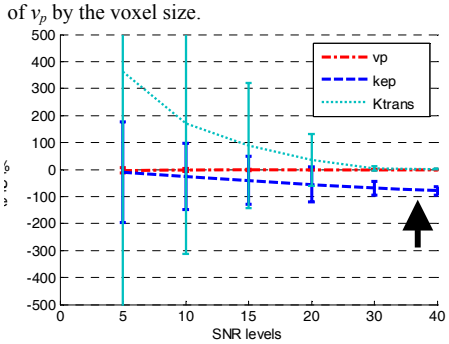

Fig. 1 Estimation errors at different SNR levels for 3 model parameters. v_p exhibited consistently high accuracy while K^{trans} showed poor precision. k_{ep} showed unexpected decreasing accuracy as SNR increased (arrow).

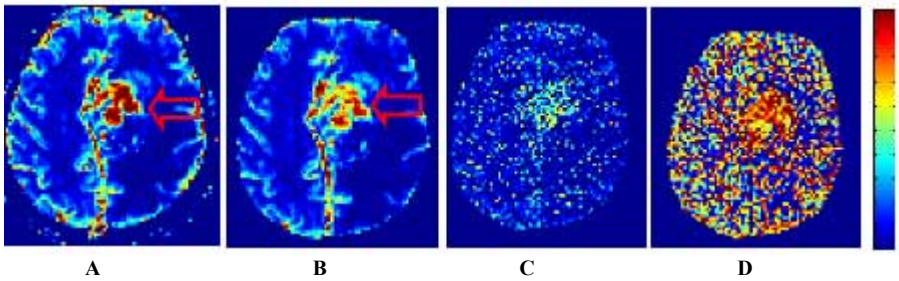

Fig. 2 Parametric maps from a patient with meningioma. A: rCBV calculated from conventional method. B: Map of v_p from FPPM model. Overestimated error seen in the rCBV map was not found in v_p map (open arrows). K^{trans} (C) and especially k_{ep} (D) maps were much noiser in both the lesion and the area of normal brain parenchyma.

Discussion and Conclusions

The importance of tumor angiogenesis has stimulated the development of techniques for simultaneous mapping of blood volume and endothelial permeability using noninvasive imaging techniques [1-3]. Our simulation assessing the precision and accuracy of the FPPM model shows that the three physiologically important pharmacokinetic parameters exhibit different sensitivities under the same circumstance of SNR. The FPPM model produces accurate measures of vascular plasma volume which shows the little variation in spite of poor SNR, consistent with the literature [1], whereas measurements from the conventional method suffer from overestimates from slow wash-out due to vessel tortuosity or second-pass transit (Figs.2A vs. 2B). As compared to the estimated maps of v_p, K^{trans} shows low tolerance of noise and k_{ep} seems inaccurate even at high SNR. While the inaccuracy of k_{ep} could theoretically be corrected retrospectively using image SNR due to high precision, the sensitivity of K^{trans} to interferences of noise would result in fitting instability, leading to failures of convergence or substantially longer processing time. These factors could become severe in nonlinear fitting, because the settings of initial points appropriate for both normal and tumor zones of the brain would be difficult to find. In conclusion, the FPPM model offers a potentially advantageous approach for simultaneous generation of the estimates of permeability and cerebral blood volume from dynamic T2*-weighted echo-planar images. However, the reproducibility of true K^{trans} and k_{ep} estimates calculated by this technique does not seem to allow pixel-by-pixel mapping under the usual image quality obtainable in routine practice. More efforts on the derivation of feasible approaches to this fitting algorithm or revision of the model should be made in future works to increase estimation accuracy for endothelial permeability.

References

1. Johnson, G., et al., MRM, 2004. 51(5): p. 961-8. 2. Li, K.L., et al., BJR, 2003. 76(901): p. 39-50. 3. Li, K.L., et al., JMRI, 2000. 12(2): p. 347-57.