Comparison of two frequently used pharmacokinetic models on the basis of simulated muscle data

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Introduction:

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) makes it possible to measure the signal change after the administration of a paramagnetic MR contrast medium (CM) with a high spatial and temporal resolution. In combination with pharmacokinetic models, it is possible to quantify functional tissue parameters characterizing different aspects of tissue microcirculation. Due to the fact that MR sequences, pharmacokinetic models and the extracted kinetic parameters vary, no direct comparison of different studies and models is possible. On the other hand, however, the increasing application of pharmacokinetic models in clinical practice makes it indispensable to analyze whether different models yield comparable results and which are the pros and cons of each model. Thus, we performed a comparison of two frequently used pharmacokinetic models developed by Tofts [1] and Brix [2] on the basis of stimulated muscle data.

Methods:

Both models are so called two-compartment models describing the complex exchange of contrast media between blood and tissue. One compartment specifies the CM concentration in the central blood pool (i.e. the arterial input function) and the other the concentration of the tissue distribution space. Bidirectional CM exchange between these two compartments is described by transfer constants. The basic assumptions made in both models are similar [3]. Differences belong primarily to the modeling of the AIF where Tofts assumes a rapid bolus injection of the CM and Brix a constant short-time infusion. Using Tofts' model one will get two fitting parameters: the volume v_e of the tissue distribution space per unit volume of tissue and the volume transfer constant K^{trans} (min^{-1}). In contrast, Brix describes the flux rate constant between tissue compartment and plasma by a rate constant k_{ep} (min^{-1}) and provides a second parameter *A*, which is directly proportional to the distribution volume (including blood volume and EES). To compare both approaches, concentration-time curves for muscle were simulated from representative measured AIFs using MMID4 (Multiple path, Multiple tracer, Indicator Dilution, 4 region model) running under the software JSIM (National Simulation Resource, University of Washington)(Fig.1). The model adaptation to an extravascular tracer allows specifying all important physiological parameters like perfusion (Pf), axial tracer diffusion in both compartments, relative plasma volume (Vp), volume of the interstitial space (Visf) and the permeability-surface product (PS). In accordance with the basic assumptions of both models, we used a representative AIF characterizing the concentration of the CM Gd-DTPA in the central blood-pool compartment after a bolus injection and a short-time infusion, respectively. Tissue simulations were performed for different values of Pf, PS and Vp. To this end, every single parameter was varied while the others stayed fixed. As initial values we used physiological parameters for healthy skeleton muscle (Pf = 0.03 ml/g/min, PS = 0.1 ml/g/min, Vp = 0.02 ml/g and Visf = 0.06 ml/g).The generated concentration-time curves were then converted into signal-time curves using the signal equation for a saturation-recovery TurboFLASH sequence [4] and noise was added (SNR = 15). Finally, the simulated "muscle" curves were analyzed with the corresponding model using the software Dynalab (Mevis, Bremen, Germany).

Results:

A significant positive correlation between k_{ep} and perfusion (r = 0.99, p<0.01) and K^{trans} and perfusion (r = 0.98, p<0.01) was found (Fig.2a). In contrast, no significant correlation between perfusion and *A* (r = -0.6177) was observed. Also v_e failed to correlate with perfusion significantly (r = 0.93). Under variation of permeability, none of the model parameters showed significant correlation. However, there was a trend of k_{ep} and K^{trans} to decrease when permeability was increased (Fig.2b). When varying Vp, a significant correlation was found with K^{trans} (r = -0.9633, p<0.01) and v_e (r = 0.9996, p<0.01) over the entire variation range, while *A* only correlated significantly in the variation range between 0.1 to 5 fold compared to standard muscle tissue (r = 0.9795, p<0.01) (Fig.2c).

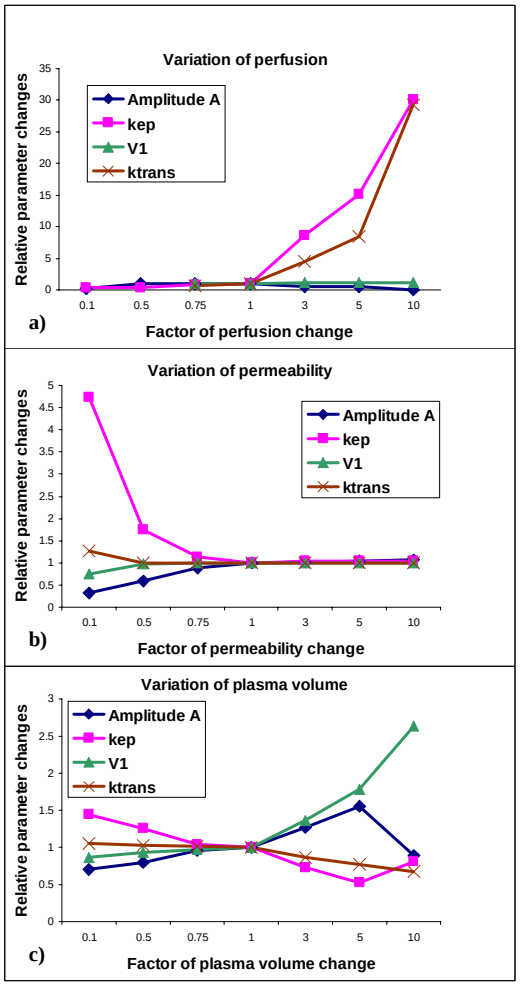

Fig. 2 *Relative parameter changes under variation of Pf (a), PS (b) and Vp (c).*

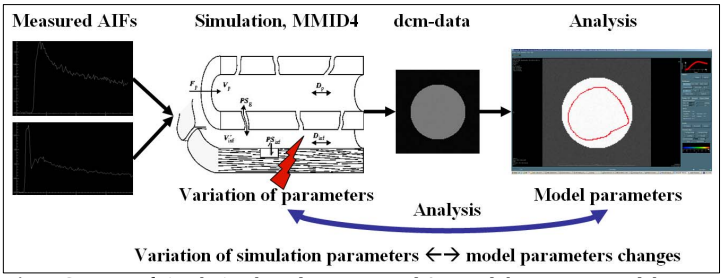

Fig. 1 *Concept of simulation based on measured AIF and the MMID4 model.*

Discussion:

First of all it should be mentioned that our simulation bases on variations of single parameters of muscle vascularisation and might not be translatable to tumors physiology in all aspects. Due to the high PS and lower Pf the model is more perfusion weighted than tumors. In general, the Tofts model seems to be more robust for extreme values but only if a sufficiently high tissue perfusion exists. For very low perfusion values (Pf = 0.015 and 0.003 ml/g/min), a fit to the data was not possible (Fig.2a). It is also shown that in muscle tissue the transfer constants (k_{ep} and K^{trans}) are predominantly affected by tissue perfusion. Changes in the transfer constants did not go in line with variations of PS and it seems that both models are not able to detect permeability changes in muscle. In contrast, both models were sensitive to changes in plasma volume. However, the *A* versus Pv curve showed a drop out at the highest chosen Pv value that might be due to fitting errors caused by the curve not having reached its maximum during simulation time yet. In summary, we could demonstrate that both models show a good sensitivity to changes in perfusion and plasma volume but a low sensitivity to permeability changes in our "perfusion weighted" skeletal muscle model. Furthermore, our data clearly demonstrates that a decrease in k_{ep} and K^{trans} in a "perfusion weighted" model does not necessarily can be interpreted as a decrease in permeability.

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References: [1] Tofts PS et al., Magn Reson Med 1991; 17: 357-367; [2] Brix G et al., J Comput Assist Tomogr 1991; 15: 621-628; [3] Tofts PS et al., J Magn Reson Imaging 1997; 7: 91-101; [4] Brix G et al., Magn Reson Med 2004; 52: 420-429