Uncertainty in the Pharmacokinetic Analysis of a Modified Reference Region Model Using Dynamic Contrast-Enhanced MRI

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Introduction

Based on a T1-weighted dynamic contrast-enhanced MR imaging (DCE-MRI), the physiological parameters, such as volume transfer constant (K^{trans}), volume fraction of extravascular extracellular space (v_e) and volume fraction of plasma (v_p), can be estimated by using a modified reference region (mRR) model including vascular term proposed by Faranesh and Yankeelov (1). The basic assumption of this model is that a reference region (RR) with stable physiological parameters, e.g. skeletal muscle, shares the same arterial supply with tissues of interest (TOI), e.g. tumor. One can estimate physiological parameters using a RR concentration curve and RR parameters when the arterial input function is unavailable. Yet, the accuracy of RR parameters, i.e. $K^{trans,RR}$, $v_{p,RR}$, and $v_{e,RR}$, may critically influence the quantification of $K^{trans,TOI}$, $v_{e,TOI}$, and $v_{p,TOI}$ (2). The aims in this study were to evaluate the effect of inaccurate assumptions on RR parameters to the physiological parameters derived from the kinetic model and the critical signal-to-noise ratio (SNR) to let RR parameters in the mRR model free to fit.

Methods and Materials

The RR and TOI curves were generated using the mTK model (2): $C_T(t) = v_{p,T}C_p(t) + K^{trans,T}\int_0^t C_p(\tau)\cdot e^{-\frac{K^{trans,T}}{v_{e,T}}(t-\tau)}d\tau$ [1], where C_T is the concentration time curves of tissue (T= RR or TOI), and C_p is a population-averaged AIF modeled by Parker et al. (3). The standard C_{RR} was simulated with $K^{trans,RR}$ = 0.08 min^{-1}, $v_{e,RR}$=0.1, and $v_{p,RR}$=0.02; a specific set of $K^{trans,TOI}$=0.25 min^{-1}, $v_{e,TOI}$=0.4, and $v_{p,TOI}$=0.06 was used for the C_{TOI} curve (1). The mRR model can be demonstrated as:

$$C_{TOI}(t) = \frac{v_{p,TOI}}{v_{p,RR}}C_{RR}(t) - \frac{v_{p,TOI}\cdot K^{trans,RR}}{v_{p,RR}^{\ 2}}\int_0^t C_{RR}(\tau)\cdot e^{-K^{trans,RR}\left(\frac{1}{v_{p,RR}}+\frac{1}{v_{e,RR}}\right)(t-\tau)}d\tau + \int_0^t\left[\frac{K^{trans,TOI}}{v_{p,RR}}C_{RR}(\tau) - \frac{K^{trans,TOI}\cdot K^{trans,RR}}{v_{p,RR}^{\ 2}}\int_0^\tau C_{RR}(u)\cdot e^{-K^{trans,RR}\left(\frac{1}{v_{p,RR}}+\frac{1}{v_{e,RR}}\right)(\tau-u)}du\right]\cdot e^{-\frac{K^{trans,TOI}}{v_{e,TOI}}(t-\tau)}d\tau \quad [2]$$

In the first part, to estimate the quantification errors caused by inaccurate input RR parameters in a mRR model, we set one of the three RR parameters with the value that is ± 10%, ± 20%, and ± 30% from its standard RR paramater and fixed the other two. The varied C_{RR} curves and literature RR parameters of $K^{trans,RR}$ = 0.08 min^{-1}, $v_{e,RR}$=0.1,$v_{p,RR}$=0.02 were used for the kinetic analysis (1). In the second part, we set RR parameters free to fit; that is, we simultaneously quantified six parameters including $K^{trans,RR}$, $v_{e,RR}$, $v_{p,RR}$, $K^{trans,TOI}$, $v_{e,TOI}$ and $v_{p,TOI}$ using the mRR model. Spoiled gradient echo (SPGR) pulse sequence based signals of SNR = 100, 150, 200, 250, and 300 were simulated. Then, the noisy signal curves were converted back to the concentration curves for kinetic analysis. Then, the all parameters were estimated by using C_{RR}, C_{TOI} curves and the mRR model (Eq.[2]). One thousand runs of each condition were simulated. The percentage mean error and coefficient of variation were calculated.

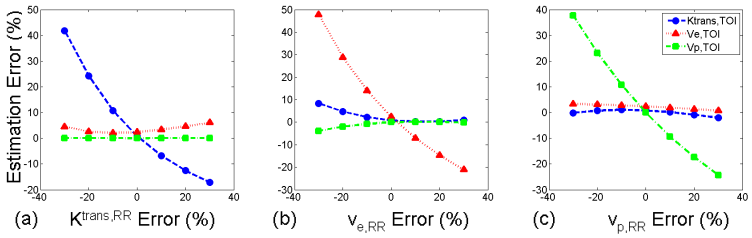

Figure 1 The estimation errors caused by inaccurate RR parameters inputs

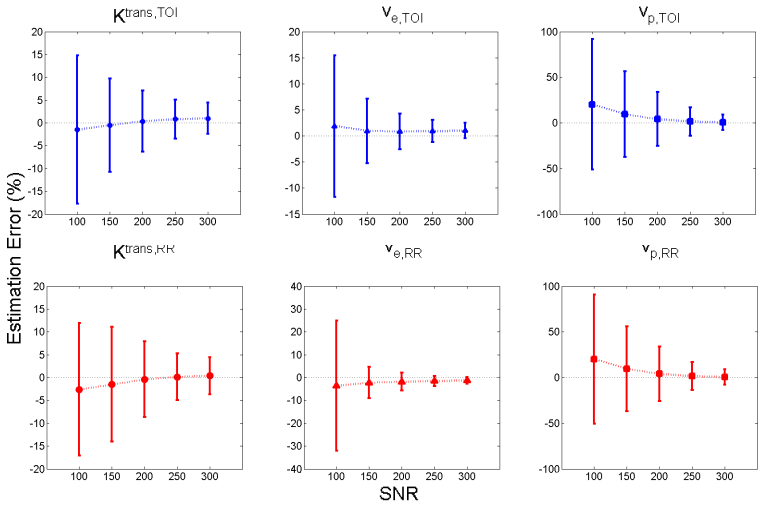

Figure 2 The estimation errors of a six-parameter-fit mRR model under varied SNRs

Results

Figure 1 showed that inaccurate RR parameters inputs can cause large estimation errors to the corresponding TOI parameters (e.g. $K^{trans,RR}$ can mainly influence $K^{trans,\ TOI}$). The results showed estimation errors of [+41.8 to -17.08], [+47.85 to -21.08], and [+37.67 to -24.33] for [-30% to +30%] variations on inaccurate $K^{trans,RR}$, $v_{e,RR}$ and $v_{p,RR}$, respectively. Figure 2 showed that the six-parameter-fit mRR model can have a less than 10% estimation errors for all parameters under SNR>300.

Discussion

From the report of Faranesh et al., the physiological parameters can have about ±20-30% variation for the skeletal muscle between individuals (4). This study showed that the phenomenon may cause large estimation errors for the quantification of TOI parameters. The applications of mRR model might be limited by the accuracy of RR parameters. One of the methods to estimate RR parameters is using a six-parameter-fit mRR model. This study suggest that this method can be applied under SNR>300 if the estimation error < 10% was required. This may not feasible for a common SPGR SNR about 10. Future work will apply this method to clinical studies.

References

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