Quantifying perfusion in conditions of rapidly changing blood flow and vascular volume: A novel tracer kinetic model

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Introduction: DCE MRI is widely used for assessing tissue perfusion noninvasively, using indicator dilution theory (1), which models tissue enhancement as a convolution between the arterial input function and impulse response function. This approach requires that the system of interest is time-invariant during data acquisition, which is fulfilled in most situations. However, the convolution approach does not work when perfusion changes dramatically during the measurement period, such as skeletal muscle perfusion during exercise-recovery. Exercise-induced hyperemia is an important index of muscle ischemia in PAD patients (2, 3). With exercise, over a few minutes, muscle perfusion can change 3-5 fold, as a result of factors such as an increase in arterial blood velocity and muscle capillary recruitment. In this study, we propose a new tracer kinetic model where both blood inflow and vascular volume can vary during the measurement. We tested the identifiability of the model parameters with numerical simulations.

Theory: For a system with a variable flow rate, the impulse response function varies depending on when the tracer is injected. For an individual transit pathway,

$$t_0 \cdot v_0 = \int_{t_{en}}^{t_{ex}} v(\tau)d\tau, \text{ then } t_0 = \int_{t_{en}}^{t_{ex}} \left(\frac{F(\tau)}{F_0} \cdot \frac{V_0}{V(\tau)}\right) d\tau \quad [1]$$

where v_0, F_0, V_0, t_0 are constant velocity, flow, vascular volume and the transit time, and t_{en} and t_{ex} are times for entry and exit for variable flow F(t). Using vascular compliance s to reflect varying vascular volume we eliminated the volumes in Eq. [1],

$$t_0 = \int_{t_{en}}^{t_{ex}} \left[\frac{F(\tau)}{F_0} \cdot \frac{1}{1+s\cdot(F(\tau)/F_0-1)}\right] d\tau. \quad [2]$$

For an impulse input, variable flow rate does not change the order that the tracers exit the system via different pathways, so the accumulated output function of constant flow and of variable flow relate by $\tilde{H}(t_{en}, t_{ex}) = H(t_0)$. Replacing t_0 by Eq. [2],

$$\tilde{H}(t_{en}, t) = H\left(\int_{t_{en}}^{t} \left[\frac{F(\tau)}{F_0} \cdot \frac{1}{1+s\cdot(F(\tau)/F_0-1)}\right] d\tau\right) \quad [3]$$

Integrating Eq. [3] for all arterial input,

$$T(t) = \int_0^t F(\tau) \cdot AIF(\tau) \cdot (1 - \tilde{H}(\tau, t))d\tau \quad [4]$$

where T is tissue concentration vs time curve from MRI data.

Hyperemia simulation: We simulated post-cuffing hyperemia of calf muscle for both healthy and severe PAD subjects. To reflect physiologically different conditions of perfusion, peak perfusion (F_P) and time to peak (TTP) parameter values were varied for a modified gamma variate function, as well as vascular compliance s (Table 1). AIF and IRF for resting state were obtained from patient data. Three levels of Gaussian noise were tested: 10%, 20% and 50% of "resting" tissue perfusion curve.

We first tested whether parameters s and variable flow F(t) can be reliably estimated from the simulated data. For comparison, conventional convolution was applied to the same data, to estimate a constant flow F^{cons}. Fitting residue, i.e. difference between data and model fit, was computed for each simulation trial to evaluate the goodness of fit.

Table 1. True parameter values and the estimates in simulation

Healthy True value	s = 0.7	TTP = 20 s	F_P = 80 ml/min/100g
Estimates (50% noise)	0.68±0.11	25.6±6.4	88.2±11.4
PAD True value	s = 0.3	TTP = 40 s	F_P = 50 ml/min/100g
Estimates (50% noise)	0.30±0.04	36.9±5.2	50.4±5.4

Results: At 10% noise level, all parameters could be estimated with less than 1% error. With 50% noise level (**Table 1**), for all parameters except for TTP of healthy subject, the standard deviations, indicating the precision, were 10%-15% of their respective true values, and the averages were less than 10% different from the true values.

Fig. 1 shows examples of curve fitting and flow estimates with the two methods. By forcing a constant flow rate, the conventional convolution approach was not able to fit the data well (residues of **61.4% and 30.1%** for healthy and for PAD, Fig 1. (a,c), dashed line), whereas the flow-varying model resulted in better fits (**7.7% and 16.9%** Fig 1. (a,c), red line)

Conclusion: We describe a novel tracer kinetic model capable of analyzing DCE MRI data acquired during conditions of varying flow and vascular volume. Beyond quantifying muscle hyperemia for PAD patients, the value of the estimating perfusion in the setting of varying flow and vascular compliance may have value in other applications as well.

References: 1. Meier and Zierler. J App Physiol 1954;6(12):731. 2. Isbell et al. JMRI 2007;25(5):1013. 3. Jiji et al. J Cardiovasc Magn Reson 2013;15:14

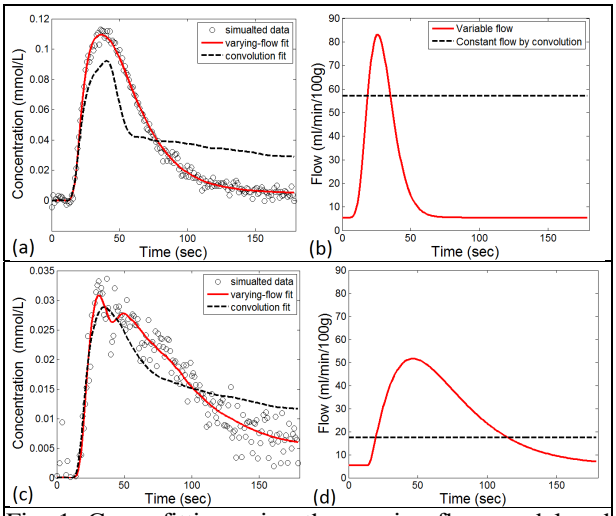

Fig. 1. Curve fitting using the varying-flow model and conventional convolution and the estimated flow for simulated healthy data (a and b), and for PAD (c and d)