In vitro validation of permeability-surface area product derived by distributed parameter model with DCE-MRI

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Introduction:

Dynamic contrast enhanced MRI (DCE-MRI) with tracer kinetic modeling has been proposed as a biomarker of tumor angiogenesis assessment in humans. Several tracer kinetic models, distributed parameter model (DP)¹, St. Lawrence and Lee model (ATH)², and conventional compartmental model (CC)³, have been proposed to calculate permeability-surface area product (PS). It was found that PS correlated with drug exposure and might predict patient outcome in an anti-angiogenic drug clinical trial.^{1,4} Recently, hollow fiber bioreactors (HFB) has been used to distinguish extravasation rates of paramagnetic CA of different molecular weights by DCE-MRI.⁵ HFB, typically used for cell culture, mimicks well the human capillary system and thus is ideal to be used to validate the microcirculatory parameters obtained by tracer kinetic modeling. The aim of this study is to validate the permeability-surface area product obtained by the DP model in a HFB.

Materials and Methods:

Hollow fiber bioreactors (HFB)

The study was performed on four types of HFB (CellMax, Spectrum Laboratories, Rancho Dominguez, CA): 410-010, 400-025, 400-012, and 400-007. The pore size diameter of the HFM is 2, 200, 300, and 500 nm, respectively. Polyethylene catheters were used to connect the HFB to a rotary peristaltic pump (Minipuls Evolution, Gilson, Middleton, WI) and a reservoir containing saline. The pump speed was set at 0.5 ml/sec for all HFBs and imaging was performed at steady state.

DCE-MRI

MRI was performed on a 1.5 Tesla scanner (Avanto, Siemens, Erlangen, Germany) using head coil (TIM, Siemens, Erlangen, Germany). A three-dimensional, fast low-angle shot (3D FLASH) sequence was used to acquire sequential images with the following parameters: repetition time TR=3.03 ms, echo time TE=1.17 ms, field of view (FOV) 40cm x 40cm, 256×256 matrix, 6 slices with slice thickness 8mm, and temporal resolution 1.38 sec. To estimate native (pre-contrast) tissue T_1 values using the dual-flip angle method, 10 sets of pre-contrast images were acquired with the above parameters for each of two flip angles, $a = 6^{\circ}$ and 18° . One milliliter of Gd-DTPA (Dotarem®, Guerbet S.A., Roissy, France) was injected at 0.5 ml/sec. This is followed by a dynamic sequence which includes 1050 consecutive sets of images acquired with the above parameters and a flip angle $a=18^{\circ}$.

Data analysis

Two slices at the centre were analyzed off-line on a Pentium IV personal computer with MatlabTM (MathWorks, Natick, MA). Region-of-interests (ROIs) consisting of the whole HFM were manually identified and ROI over input tubing was used as arterial input function (AIF), as shown in Fig. 1. The input function and the HFM concentration function was fitted into the DP model, ATH model, and CC model to obtain the permeability-surface area product. The calculated PS was plotted against the pore size area of each HFM and Pearson correlation coefficient was computed.

(a)

Results:

Fig. 1 shows a linear relationship between PS derived from DP, ATH and CC models and pore size area.

0.15

0.1

0.05

0

0.05

0.1

Pore area (mm²)

Conclusion:

The result shows correspondence between calculated PS from all 3 models and pore size area and might validate the usefulness of these models in the clinical settings. Similar experiments in mice will be done then to further validate the distributed parameter model.

Limitations: (1) Limited range of pore size diameter of the commercially available HFM, (2) Non-physiological value and shape of the AIF due to difference in compliance of the vein and the tubing, and (3) Pore density uniformity assumption for all HFBs.

References:

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3. Brix G, et al. Radiology 1999; 210:269-76.

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Fig 1. (a) Hollow fiber bioreactor, (b) MRI image of the HFB, and plot of PS from each model against the pore size area in (c) DP, (d) ATH, and (e) CC.



(b)

Hollow fiber bioreacto

Hollow fiber bioreactor

y = 0.5876x

R² = 0.9762