**Transfer constant and plasma volume fraction in dynamic contrast enhanced magnetic resonance imaging: different dependencies on tumor model, size, and antivascular treatment**

T. Nielsen[1,2], R. J. Maxwell[3], H. Stødkilde-Jørgensen[4], L. Østergaard[1], M. R. Horsman[2]

[1]Department of Neuroradiology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, [3]Gray Cancer Institute, Northwood, United Kingdom, [4]MR Research Center, Aarhus University Hospital, Aarhus, Denmark

Introduction: Combretastatin A-4 disodium phosphate (CA4DP) is a leading vascular disrupting agent in clinical trials[1-3]. CA4DP induces vascular damage and necrosis with variable efficacy in different tumor models[4]. Dynamic contrast enhanced magnetic resonance imaging (DCEMRI) allows in vivo characterization of tumor vasculature, and a standardized tissue model based on Toft's model is widely used including or not including plasma volume fraction[5]. The purpose of this study was to characterize the microvasculature in two tumor models responding differently to CA4DP before and after CA4DP treatment at two tumor sizes.

Methods: The tumor models used were the C3H mammary carcinoma at 200 $mm^3$ (n=6) and 800 $mm^3$ (n=6), and the KHT sarcoma at 200 $mm^3$ (n=7) and 800 $mm^3$ (n=7) grown in the right rear foot of female CDF1 and C3H/km mice, respectively. CA4DP was administered i.p. at a dose of 100 mg/kg. DCEMRI was performed on a 7 T spectroscopy/imaging system (Varian, Palo Alto, CA) before and 3 hours after CA4DP administration. The MRI protocol included measurement of precontrast $T_1$ values for determination of contrast agent concentration in the dynamic series using an inversion recovery sequence, and acquisition of 100 dynamic $T_1$-weighted images with 6 s time resolution from a central 2 mm tumor slice using a fast gradient echo sequence. The contrast agent Gd-DTPA (Magnevist, Schering, UK) was infused in the dosage 0.1 mmol/kg during the initial 4 s of the sixth image acquisition. From the concentration-time curves, the semiquantitative parameter initial area under the curve (IAUC) for the initial 90 s post contrast was calculated, and Toft's model including a vascular term was applied for estimation of the transfer constant $K^{trans}$ and plasma volume fraction $v_p$. The tumor models were compared with respect to median map values of the estimated parameters and their relative change by one-way analysis of variance.

Results: Figure 1 shows maps of an 800 $mm^3$ C3H tumor, and Figure 2 shows mean±1SE of the initial map median values for each tumor and size. Initial IAUC was tumor dependent for 200 $mm^3$ tumors (p=0.047) and for all tumors (p=0.026). Initial $K^{trans}$ was size dependent for C3H tumors (p=0.001) and for all tumors (p=0.002), and tumor dependent for 200 $mm^3$ tumors (p=0.021). Initial $v_p$ was tumor dependent for 200 $mm^3$ tumors (p=0.025), 800 $mm^3$ tumors (0.012), and all tumors (p<0.0005). The only significant difference in treatment induced relative change was the tumor dependency of relative $v_p$ change for all tumors (p=0.031).

Conclusions: The two tumor models investigated showed different microvascular characteristics and different microvascular response to CA4DP as evaluated using DCEMRI. Inclusion of the vascular term in the model separated plasma volume from blood flow and permeability, and thus further explained differences in the microvasculature of the two tumor models.

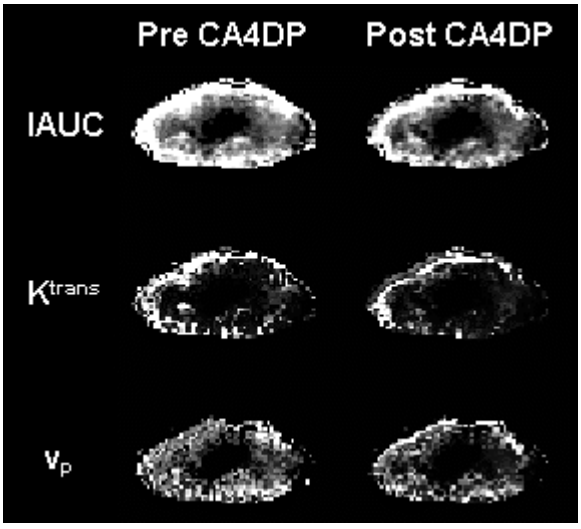


Figure 1: Maps of an 800 $mm^3$ C3H tumor. From top: IAUC, $K^{trans}$, and $v_p$. Left: pre treatment, right: post treatment.

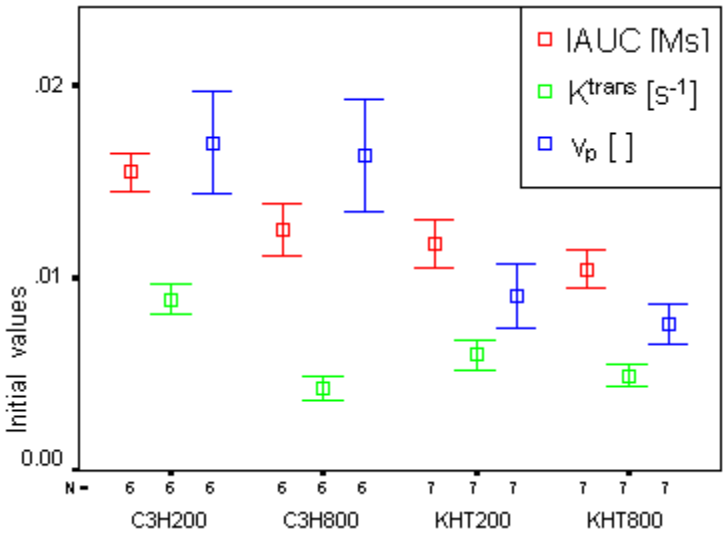


Figure 2: Initial IAUC, $K^{trans}$, and $v_p$ values (mean±1SE) for the C3H tumor and the KHT tumor, both at the sizes 200 $mm^3$ and 800 $mm^3$.

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