MR imaged characteristics of tumor angiogenesis depends on molecular size of contrast agents

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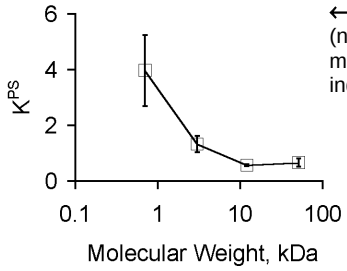
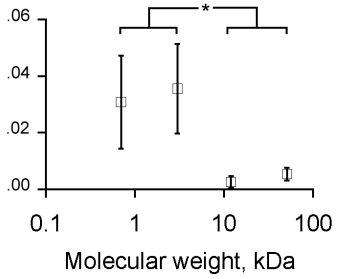
INTRODUCTION: Dynamic contrast-enhanced MR imaging with application of pharmacokinetic models renders parameters, such as endothelial transfer coefficient (K^{PS}), blood flow (F_p) and plasma fraction (f^{PV}), that may be used as surrogate markers for tumor angiogenesis [1]. Endothelial transfer coefficient, blood flow, and permeability-surface area-product (PS) are related by $K^{PS} = F_p(1-\exp(-PS/F_p))$. This shows that for large molecules with a moderate permeability (i.e. when $PS<<F_p$) K^{PS} is nearly equal to the product "PS" and for decreasing molecular size K^{PS} becomes flow dependent, which is the case for clinically approved Gadolinium (Gd) based contrast agents. To optimize imaging, various investigators compared the use of different contrast agents [2,3]. However, the resulting question "which contrast agent size is the best?" could not be satisfactorily answered, because molecular composition and paramagnetic properties of contrast agents that have been compared to date (Gd chelates, Gd conjugated with linear polymers or albumin, and iron-oxide particles) [1-3], were too different. Gd based dendrimers are well defined monodisperse contrast agents that can be produced by a stepwise synthesis process to create contrast agents with different molecular size but equal chemical composition [4]. The aim of the present study was to compare the use of Gd based dendrimers in a range of molecular sizes that could be realistic for (future) safe application, for dynamic contrast-enhanced MR imaging of tumor angiogenesis.

METHODS: Gd based contrast agents with molecular weights of 0.7, 3.0, 12.0 and 51.0 kDa were synthesized by conjugating Gd and the chelating moiety DTPA with different sizes of polypropylene imine dendrimers [4]. A mouse tumor (LS 174T) model [2] was used for MR imaging with one of the four sizes of contrast agents; n=4 mice per contrast agent. MR imaging was performed at day 16 after tumor inoculation using a 1.5T system (Philips, ACS-NT). The imaging protocol included a pre-contrast T_1 measurement and T_1-weighted dynamic contrast enhanced series (3D-FFE, TR 50 ms, TE 7 ms, FA 35°, voxel size 0.5×0.5×2 mm) with slow injection of contrast agent into the tail vein (0.03 mmol Gd/kg). Application of a 2-compartment model [2] yielded transfer coefficient (K^{PS}, min^{-1} / 100 cm^3 of tissue) and plasma fraction (f^{PV}, ml / cm^3 of tissue) values for each voxel in a central slice through the tumor. Values and spatial distributions of K^{PS} were analyzed as a function of molecular weight.

RESULTS: A significant inverse relationship (Spearman r = -.72, P = .002) was observed between magnitude of tumor K^{PS} and molecular weight (Fig 1). Figure 1 also illustrates that variations between animals in K^{PS} increases for smaller molecules. Histogram analysis (Fig 2) revealed that the width of the distribution (i.e. second moment) of K^{PS} values showed an inverse relationship with the molecular weight (Spearman r = -.80, P < .001). Plasma fraction values were significantly (P = .03) higher (Fig 3) with use of small molecular (0.7 and 3.0 kDa) agents as compared to large molecular (12.0 and 51.0 kDa) agents.

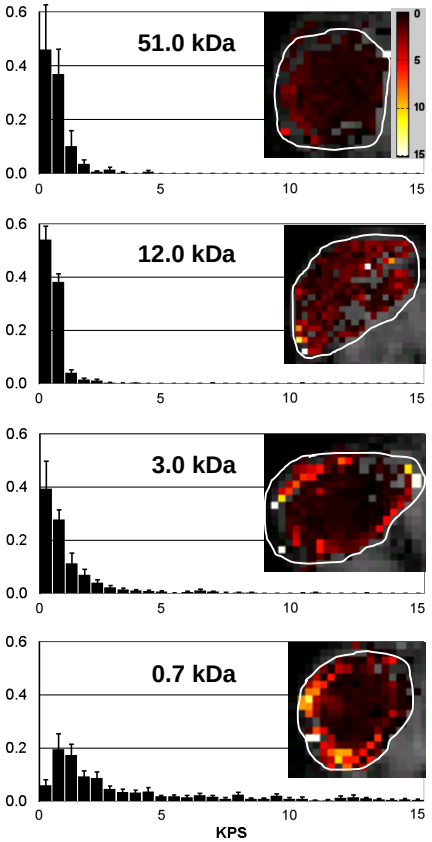


← **Fig 1:** Average tumor K^{PS} (n = 4 per group) versus molecular weight; error bars indicate SEM.



→ **Fig 3:** f^{PV} versus molecular weight; * indicates significant difference between small and large molecules, P = .03.

Fig 2: Normalized histograms of the spatial distribution in K^{PS} (± 250 pixels per tumor) for each contrast agent. Note the wider range in K^{PS} for the smaller molecules.



DISCUSSION: Angiogenic microvasculature in malignant tumors is characterized by increased microvessel permeability, increased numbers of microvessels, and increased level and heterogeneity of blood flow. K^{PS} rapidly decreases with increasing molecular size. Our results show that K^{PS} varies the least with molecular size for large molecular contrast agents, which is most likely to reflect pure microvessel permeability (-surface-area-product). In contrast, higher K^{PS} values measured for smaller molecules yield inhomogeneous spatial distributions that are caused by the influence of *heterogeneous* flow on the K^{PS}. Easy extravasation and movement through interstitial matrix of small molecules compared to large molecules explains overestimation and large variations in f^{PV} values with use of small molecules.

CONCLUSION: Dynamic contrast-enhanced imaging of tumor angiogenesis yields different tumor microvasculature characteristics depending on the molecular size of the contrast agent. Plasma fraction values are grossly overestimated with increased variation when using small molecular (< 3 kDa) contrast agents. Uncontaminated microvessel permeability is best measured with the use of larger molecular agents (> 12 kDa). Whereas, K^{PS} values measured with smaller molecules (< 3 kDa) reflect a combination of permeability and heterogeneous microcirculatory flow, which are both characteristic properties of tumor angiogenesis.

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