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Title: Analysis of the effects of tumour vascular targeting drugs on the vascular permeability of experimental tumours through multiphoton microscopy.

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Abstract: This work aims to develop analytical techniques for measuring vascular permeability in experimental tumours and to determine the effect of the tumour vascular damaging agent, *combretastatin A-4-phosphate* (CA-4-P), on tumour vascular permeability to a high molecular weight contrast agent.

Multiphoton fluorescence intravital microscopy was used to acquire 3D images of the leakage of 40 kDa FITC labelled dextran from the blood vessels of rat P22 sarcomas growing in dorsal skin flap 'window chambers' in BDIX rats. Images of a region of interest in each tumour were acquired over a time-course of 1-2 hours following intravenous administration of FITC dextran in anaesthetized rats (n=9 for CA-4-P 30 mg/kg; n=6 for saline treated controls). Image processing techniques were used to quantify the intensity of fluorescence as a tissue/vessel ratio (Cp/Ct). The images were noisy, with spatial deformations. Traditional analysis techniques involved hand segmentation and selection of ROIs, this is labour intensive and unreliable. A semi-automated method was used: a double threshold determines vessels and tissue, boundaries were determined through convolution with Gaussian kernels, data was corrected in time with rigid and non-rigid deformations, noise was removed, and average intensity of the ROI was obtained for each time sample. Treated and control groups were statistically different ($p=0.0012$) and it was observed that Cp/Ct was higher for the treated group than for the controls. 'Patlak' plots were used to determine the leakage parameter k2 from the kinetic data. k2 is closely related to the product of the permeability constant, P, and the vascular surface area for exchange, S. Again, the Patlaks provided statistical discrimination ($p=0.016$). Both Cp/Ct and k2 values indicate that CA-4-P damages the barrier function of tumour blood vessels, increasing vascular permeability. This is likely to play a major role in CA-4-P-induced tumour blood flow collapse. Funded by CR-UK.