Quantitative estimates of tissue perfusion using simple initial upslope measures in DCE-CT and DCE-MRI

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Mathematical models based on CT and MRI dynamic contrast-enhanced imaging data have become essential tools for the purpose of quantification of organ perfusion. Although several well-established mathematical models have been introduced for the analysis of dynamic contrast-enhanced data, the application of microsphere theory (also known as the upslope method - USM) has attracted the attention of many authors, mainly due to its simplicity and speed of application, which makes it attractive for use in the clinical environment.

AIMS:

The aims of the current study were: (1) To investigate the validity of perfusion measurements for normal and pathological tissues (normal brain, prostate and brain and prostate tumours) using the USM in dynamic CT and MR imaging from computer simulations in non-leaky and leaky capillaries and (2) To explore the effects of signal to noise and injection rate on the accuracy of these perfusion estimates.

METHODS:

Data for arterial input (AIF) curves was generated from human DCE-CT and DCE-MRI datasets (6 brain and 13 prostate) and smoothed using a combination of 3 gamma variate functions. Curves modelling tracer tissue uptake were constructed from the AIF and the AATH model[1] using Monte Carlo simulations (81 curves for brain and prostate in total). The parameters used to construct the synthetic data were: tissue perfusion (*F*), fractional plasma volume (v_p), tracer extraction fraction (*E*) and fractional extracellular extravascular volume (v_e). Standard values for perfusion and blood volume for brain[2] and prostate[3] were chosen from pre-existing PET studies using labelled water or carbon monoxide. The extraction fraction coefficient and the interstitial volume were chosen from previously published studies using MRI with a range representative of the outer limits of the physiological values in the literature. In the brain data *E* values ranged between 0 (for healthy brain) and 0.75 (aggressive tumoral tissues) and in prostate between 0.5 and 0.9. The choice of interstitial volume estimates was also based on previous publications and designed to cover the entire reported range of values in both normal[2] and pathological[4,5] tissue. The range of the interstitial space values was 0.10 – 0.40 ml/ml of tissue in brain (lower limit close to normal brain tissue, the upper limit aggressive tumour) and 0.30 – 0.60 ml/ml of tissue in prostate (**Table 1**).

BRAIN				PROSTATE			
F	V_p	E	V_e	F	V_p	E	V_e
0.22	0.02	0.00	0.10	0.15	0.05	0.70	0.30
0.44	0.04	0.25	0.20	0.08	0.03	0.50	0.15
0.66	0.06	0.75	0.40	0.30	0.08	0.90	0.60

Table 1. *Perfusion (F – ml/min/g tissue), fractional plasma volume (V_p – ml/ml tissue), extraction fraction (E) and fractional extracellular extravascular volume (V_e – ml/ml tissue) used in simulations.*

The USM was then applied to the simulated curves and tissue perfusion values were estimated by the ratio of the steepest tissue gradient to the peak of the smoothed AIF curve. Finally, comparison was made between the actual and estimated perfusion values.

The influence of noise on the accuracy of perfusion calculations was investigated by progressively adding Gaussian noise with zero mean and unit variance to both the arterial and tissue uptake curves. In order to examine the effects of the injection rate on the accuracy of the estimated tissue perfusion, wider AIFs (area under the curve corrected) were generated by convolution of the original AIF with top-hat functions with widths of 5s, 10s, 15s, and 20s.

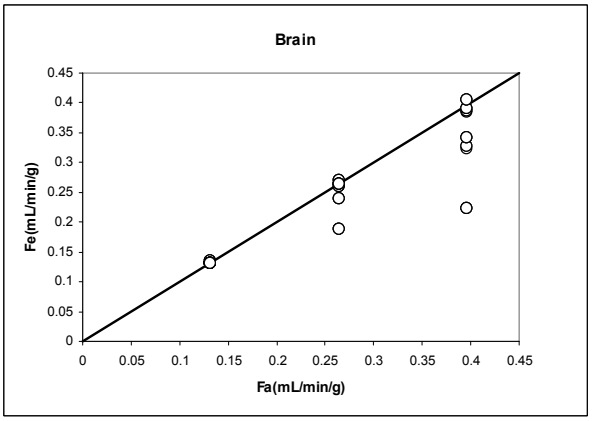

Figure 1. *Comparison between actual (F_a) and estimated (F_e) abnormal brain perfusion values (E>0). The solid line is the line of identity.*

RESULTS:

Correlation analysis for non-leaking capillary bed (E = 0) showed moderate correlation between the USM estimated and actual input perfusion ($r = 0.78$; $p \leq 0.05$). The correlation coefficient improved for a leaky brain tumour capillary bed ($r = 0.91$; $p \leq 0.001$). A strong correlation ($r = 1$; $p \leq 0.001$) between estimated and actual perfusion was also found for prostate data in the case of E> 0 (leaky capillary). The relationship between actual and estimated perfusion values in brain tumours is presented in **Figure 1**.

Monte Carlo simulations examined the contribution of noise to the accuracy of the estimated perfusion using USM. Our simulations showed that perfusion measurement accuracy increases as noise decreases (SNR increases). In addition, decreases of the SNR also cause overestimation of perfusion and, as such, the steepest gradient must be measured within a time interval around the AIF peak.

Percentage error of the estimated perfusion values was shown to decrease with increases in transit time, which is in agreement with the assumptions of the microsphere model. An increase in the width of the arterial curve decreases the estimated perfusion accuracy. For short transit times and broad arterial curves, there is insufficient time for the bolus to be wholly confined within the tissue and, hence, the steepest gradient is not established before washout takes place of some of the tracer. This leads to underestimation of perfusion.

CONCLUSIONS:

The USM can be successfully used to calculate perfusion in normal and pathological tissues (normal brain, prostate and brain and prostate tumours) and is most accurate in tissues with relatively long transit times (leaky capillaries). Its accuracy can be improved with the use of a rapid injection (sharp AIF). Increased image noise causes overestimation of perfusion and, therefore, using data with good SNR is essential to producing accurate perfusion values.

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