Use of An Individually Measured Hematocrit in DCE-MRI studies

C. Roberts\textsuperscript{1,2}, S. Hughes\textsuperscript{3}, J. H. Naish\textsuperscript{1,2}, K. Holliday\textsuperscript{1,2}, Y. Watson\textsuperscript{1,2}, S. Cheung\textsuperscript{1,2}, G. A. Buonaccorsi\textsuperscript{1,2}, H. Young\textsuperscript{4}, N. Clarke\textsuperscript{5,6}, and G. J. Parker\textsuperscript{1,2}

\textsuperscript{1}Imaging Science and Biomedical Engineering, The University of Manchester, Manchester, Greater Manchester, United Kingdom. \textsuperscript{2}Biomedical Imaging Institute, The University of Manchester, Manchester, Greater Manchester, United Kingdom. \textsuperscript{3}Paterson Institute for Cancer Research, The University of Manchester, Manchester, Greater Manchester, United Kingdom. \textsuperscript{4}AstraZeneca, Macclesfield, Cheshire, United Kingdom. \textsuperscript{5}Department of Urology, Salford Royal Hospital NHS Foundation Trust, Salford, Greater Manchester, United Kingdom

Introduction

Dynamic contrast-enhanced MRI (DCE-MRI) is commonly applied in early-phase drug development to quantify tumor microvascular characteristics through the application of a tracer kinetic model to estimate parameters such as $K_{trans}$ (contrast agent transfer coefficient, a composite of blood flow and capillary permeability) and $v_p$ (blood plasma volume). An important influence on DCE-MRI parameters that is commonly overlooked is the hematocrit (Hct), which relates the measured whole blood contrast agent concentration to the blood plasma contrast agent concentration, thereby influencing the arterial input function ($C_a$), $K_{trans}$ and $v_p$. In most DCE-MRI a fixed global value for Hct is assumed (Hct\textsubscript{G}). However, in cancer patients where the Hct level may be reduced [1], for example as a result of pathophysiological processes or drug induced effects, using an assumed value for Hct will lead to error in estimates of $K_{trans}$ and $v_p$. In this study we investigate the magnitude of errors caused by assuming Hct when the true measured Hct (Hct\textsubscript{m}) is known.

Methods

Imaging: 13 patients with advanced prostate cancer and bone metastases were imaged at 1.5 T using a Philips Achieva (Philips Healthcare, Best, The Netherlands) MR scanner on up to 5 separate occasions (2 baseline visits and 3 post-treatment) as part of a clinical trial. The DCE-MRI protocol used an axial 3-D spoiled gradient echo (FSE/SPGR) sequence with baseline $T_R$ measured using the variable flip angle method [2] with the following parameters: $2^\circ$, $10^\circ$ and $20^\circ$ flip angles, TR/TE = 3.0/0.82 ms, FOV = 375 x 375 mm$^2$, matrix = 160 x 160, slices = 25, thickness = 4 mm. The dynamic image acquisition used the same parameters with a flip angle of $20^\circ$, $130$ dynamic timepoints and a temporal resolution of 4.6 s. On the sixth dynamic timepoint, 0.1 mmol/kg of body weight of 0.5 mmol/ml Dotarem (Guerbet, France) was administered through a Spectris power injector (Medrad Inc.) at a rate of 3 ml/s followed by an equal volume of saline flush also at 3 ml/s.

Initial DCE-MRI analysis: Regions of interest (ROI) were defined for the whole tumor volume within the bone. Enhancing voxels were identified and the extended Kety model [3] was fitted to each voxel’s time series using an automated arterial input function measurement [4]. Hct\textsubscript{G} was set as 0.42 in the initial analyses. 3D maps of $K_{trans}$, $v_p$ and $v_p$ were generated and summarized using median ($K_{trans}$, $v_p$) and mean ($v_p$) summary statistics for each tumor.

Hct measurement: Whole blood was collected in standard EDTA tubes immediately prior to each DCE-MRI scan. Samples were processed using an automated analyzer (Advia 2120, Siemens, Germany) and the Hct was calculated as [red cell count (/L) x mean cell volume (fL)].

Correction using Hct\textsubscript{m}: $K_{trans}$ and $v_p$ parameters derived using Hct\textsubscript{G} in the initial analyses were corrected by scaling by (1-Hct\textsubscript{m}/(1-Hct\textsubscript{G})).

Results

Hct\textsubscript{m} values for all patients and timepoints throughout the study were systematically lower than the Hct\textsubscript{G} of 0.42. The Hct\textsubscript{m} show inter-visit variation in each patient and also between patients (Fig. 1), with Hct\textsubscript{m} values ranging from 0.213 to 0.401. The errors in $K_{trans}$ and $v_p$ parameters as a result of using the Hct\textsubscript{G} value in the analysis range from -3% to -27% (Fig. 1).

Discussion

This study has demonstrated the magnitude of potential errors in tracer kinetic parameters when using an assumed value for Hct, rather than an individually measured Hct. These findings have implications for clinical trials where a treatment effect may be masked due to the fluctuations in patients’ Hct throughout a course of therapy not being accounted for. Large fluctuations in Hct\textsubscript{m} were observed not only within each patient in this intervention study but also between the patients – the mean (1-Hct\textsubscript{m}) shows this in Fig. 1a. This is of importance if DCE-MRI parameters are used to understand inter-patient differences (for example when predicting response to therapy). In recent years, much work has been done to minimise AIF-related errors in DCE-MRI studies, such as correcting for blood inflow, B\textsubscript{i} inhomogeneity [5] and optimising temporal resolution. Our results demonstrate that the errors that can be caused by neglecting Hct measurements in patient studies are of a similar magnitude to or greater than other sources of error, indicating that Hct measurement should be included as standard for all patient visits.

References