

INTER-OPERATOR VARIABILITY IN PERFUSION ASSESSMENT OF TUMORS IN MRI

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ABSTRACT

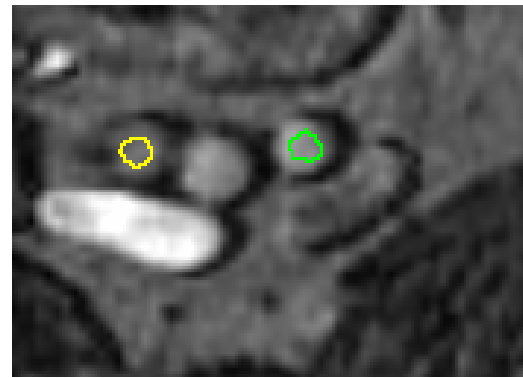
A method is presented for the calculation of perfusion parameters in dynamic contrast enhanced MRI. This method requires identification of uptake curves for both tumor tissue and plasma. Inter-operator variability in the derived rate constant between plasma and extra-cellular extra-vascular space is assessed using semi-automated tumor margin identification with both manual and automated plasma identification. In addition, an assessment is made of the contribution to total variability made by differences in tumor margin identification and differences in plasma identification. Experimental results show a mean coefficient of variability (CV) for parameter measurement with manual plasma identification of 20.1%, with a mean CV for parameter measurement with automated plasma identification of 6.7%. Analysis shows that 67% of the variability in parameter measurement with manual plasma identification is attributable to differences in identified plasma signal, with the remainder attributable to differences in identified tumor margins.

1. INTRODUCTION

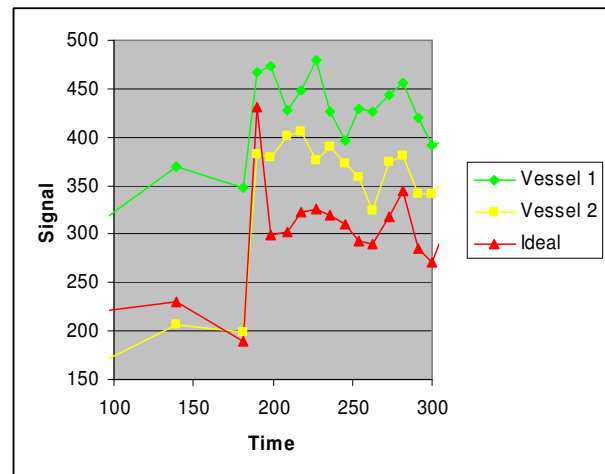
Dynamic contrast enhanced MRI (dceMRI) has demonstrated considerable utility in both diagnosing and evaluating the progression and response to treatment of malignant tumors [1,2]. dceMRI involves the periodic acquisition of T_1 -weighted images before, during and after injection of a gadolinium labeled tracer such as gadopentetate dimeglumine. The change over time in signal intensity in a voxel or region of interest in this time series can then be related to tracer concentration. By making use of a two-compartment model, with one compartment representing blood plasma and the other abnormal extra-vascular extra-cellular space (EES), the observed uptake curves in tissue and plasma can be used to estimate various physiological parameters [3,4,5].

The parameter of primary interest in this work is the volume transfer constant between blood plasma and EES, commonly referred to as K^{trans} [3]. This parameter is related to both blood flow and endothelial permeability, and is therefore a good endpoint for estimating the blood supply available to a target malignancy.

One of the primary challenges in estimating perfusion parameters is identifying an accurate plasma uptake curve. Using a theoretical curve ignores differences in injection rate and cardiac output, which can greatly reduce reproducibility. However, the MR signal in arteries is frequently corrupted by flow artifacts, with the result that regions of interest at different points in the same artery or in other nearby vessels can provide grossly different uptake curves. This problem is illustrated in Fig. 1.



(a)



(b)

Figure 1: (a) One section from Subject 1 Time 1 with two small arteries identified as separate ROIs. (b) Raw uptake curves for the regions in (a), with an automatically identified ideal plasma signal.

Note that in Fig. 1 above, vessel 1 and vessel 2 show significantly different uptake curves. Moreover, neither vessel shows the distinctive sharp peak and subsequent plateau characteristic of plasma enhancement following injection of a tracer bolus.

We have developed a method for the identification of an optimized plasma signal, described below, which is intended to eliminate this source of measurement variability and thereby increase the sensitivity to change of perfusion parameter measurements. The uptake curve generated by this method is shown in red in Fig. 1 (b). Note that this curve shows a greater enhancement peak than that of either vessel, a smoother plateau, and a more characteristic shape. The primary purpose of this study was to assess the utility of this automated plasma identification technique with respect to that of the currently accepted method of manual plasma identification.

2. MEASUREMENT TECHNIQUES

Tumor margins were identified in this study using Geometrically Constrained Region Growth (GEORG) [6,7]. This technique requires a user to place a seed or string of seeds within each desired structure throughout the volume using one or more mouse clicks. The seed regions then expand into neighboring voxels provided that two constraints are satisfied: the grayscale value of the neighboring voxel must have a high probability of falling within the statistical distribution defined by all currently included voxels, and inclusion of the neighboring voxel must not cause the shape of the included region to deviate excessively from the *a priori* regional shape model. Once initiated, the expansion process continues until a stable boundary has been established. The resulting contour is then converted into a *snake* [8,9] which can be interactively corrected by the analyst if the initial result is sub-optimal.

After identifying the tumor margins, the analysts were required to identify a region of plasma, preferably in an artery in close proximity to the tumor. This was done using manual tracing with a computer mouse. At this point, the identified plasma region was used for parameter calculation, as described below. In addition, the identified plasma region was used to initialize an automated search algorithm whose intent was to identify an optimized plasma signal for the data set under consideration. Each voxel in the data set was assigned a score based on time point of maximum uptake, slope at maximum uptake, peak value, and conformance to a gamma variate curve. The highest scoring twenty-five voxels in the data set were then assigned to the ideal plasma region of interest.

After plasma had been identified by either manual or automated means, uptake curves were generated for both tumor and plasma. These were designated $C_t(t)$ and $C_p(t)$, respectively. In the interests of noise reduction, both plasma and tumor data were fit to gamma variate curves. The vascular bed was modeled as a linear system, such that:

$$C_t(t) = C_p(t) * h(t) \quad (1)$$

with impulse response $h(t)$ given by:

$$h(t) = K^{trans} e^{-k_{ep}t}, \quad (2)$$

where k_{ep} is the rate constant between the EES and blood plasma. Given $C_t(t)$ and $C_p(t)$, K^{trans} and k_{ep} were estimated using a gradient-descent energy minimization scheme. Local minima were avoided through the use of multiple instantiations with different initial parameter settings.

3. EXPERIMENTAL PROCEDURE

The experiments involved in this study were intended to assess the reproducibility of perfusion measurements using manual and automated plasma identification, and to determine the percentage of measurement variability due to differences in tumor margin and plasma region of interest, respectively. Experimental data were derived from three dogs with naturally occurring mammary tumors. Each animal was imaged three times over a period of 12 weeks. Images for this study were acquired using a GE 1.5T LX/CV scanner. Three slices through each tumor were acquired using a cardiac coil. Perfusion images used a GRE pulse sequence with a repetition time of 20ms, echo time of 1ms, and a flip angle of 40 degrees. Imaging time for each image set was seven seconds, with a two second scanner delay, yielding temporal resolution for the data set of nine seconds. The reconstruction matrix was 256x192, FOV was 140mm, and slice thickness was 4mm. A sample image from this data set is given in Fig. 2.

Because a primary aim of this study was the assessment of inter-operator variability, four analysts were trained in the use of the analysis software. All analysts were also trained in the appearance of canine mammary tumors and the selection of appropriate plasma regions using images from animals not included in this study. Each analyst was then asked to identify and delineate both tumor and plasma in each of the nine included data sets. When identifying plasma, the

analysts had the option to view the uptake curve for the currently selected region at any time, and to erase, modify or replace the currently selected region. In this way each analyst was able to manually select a reasonably optimized plasma region.

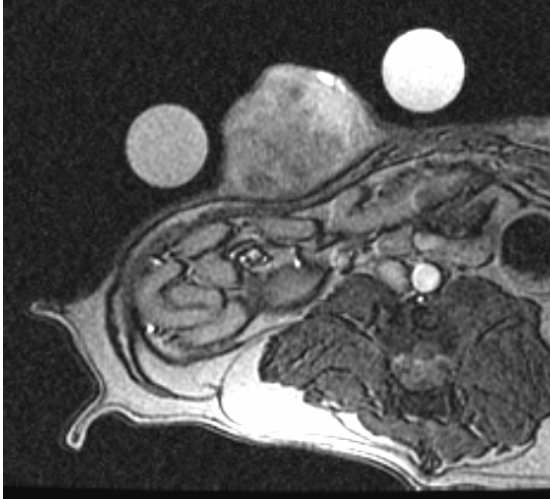


Figure 2: A sample image from the perfusion data set for Subject 3 at Time 2. The circles on either side of the tumor are phantoms. These were worn on a belt around the animal during imaging and were used for motion estimation and correction.

Once all regions of interest were delineated, K^{trans} values were calculated first using the regions of interest as identified by the analyst, and then using the analyst's tumor identification with the automatically identified plasma uptake curve. By comparing the variance seen between analysts using manually identified plasma with that seen between analysts using the automatically identified plasma, which was identical across analysts, it was possible to isolate variability related to plasma signal from that related to differences in tumor margin identification.

4. EXPERIMENTAL RESULTS

Coefficients of variability in measurement of K^{trans} among the four analysts, defined as measurement standard deviation divided by measurement mean, were calculated separately for manual and automatic plasma identification, and for each of the nine cases examined. For the nine manual plasma identifications, coefficients of variability ranged from 3.1% to 39.2%, with a mean of 20.1% and a median value of 21.5%. For the nine automated plasma identifications, coefficients of variability ranged from 3.1% to 11.8%, with a mean of 6.7% and a median value of 6.2%.

Bearing in mind that the same tumor margins were used for both the automated and manual plasma calculations, it can be generally surmised that approximately two thirds of the variability seen in the manual measurements was a result of differing plasma signal identifications, with the remaining one third attributable to differing tumor margin identifications. It should be noted that the variability attributed to differences in tumor margins is similar to that reported previously for volume measurements of lung tumors using GEORG [6].

An examination of a scatterplot of K^{trans} measurements using manual vs. automatic plasma identification (see Fig. 3) shows that the correlation between the two measures is reasonable given the high variability of the manual measurements. It also shows a slope of 0.874, indicating that on average the manual measurement gives a somewhat higher estimation of K^{trans} than the automatic measurement. This is as expected, since the general effect of flow artifacts will be to reduce the apparent plasma enhancement, thereby exaggerating the proportion of tracer apparently passing into the EES.

An examination of the trend over time in K^{trans} for subject 1 (see Figs. 4 and 5) using manual and automated plasma identification highlights the value of the reduced measurement variability afforded by the automated process. Although both trend lines indicate that vascular perfusion for this tumor is declining over time, higher variability makes that assumption statistically insupportable at time two for manual plasma identification, and marginally supportable after time three. Using automated plasma identification, however, this subject may be confidently classified as declining after time 2.

5. DISCUSSION

Manual plasma identification for perfusion parameter calculation is currently standard practice for both clinical and experimental purposes. The results of this study indicate that increased accuracy and sensitivity to change could be achieved by making use of an automated method for plasma identification such as the one described here.

It should also be noted that the difficulty of identifying a suitable plasma signal is typically greater in smaller animals such as the dogs used in this study than in humans. This is due to small animals' higher blood velocity, which exaggerates flow artifacts in the arteries, as well as to the lower signal to noise ratio that is achievable when imaging smaller anatomy. The values

given in this work for parameter variability due to differences in plasma identification should be considered an upper limit when estimating likely variability in human studies.

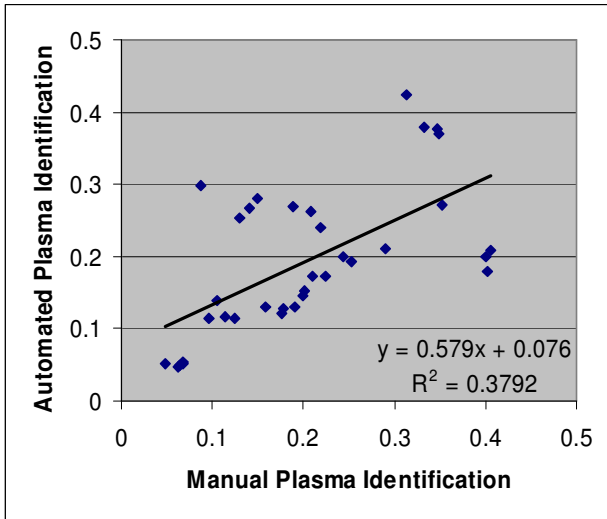


Figure 3: A scatterplot of K^{trans} values using manual and automatic plasma identification. Correlation is reasonable considering the high variability of the manual measurements. The slope indicates that manual measurements are on average higher than automated ones, as expected.

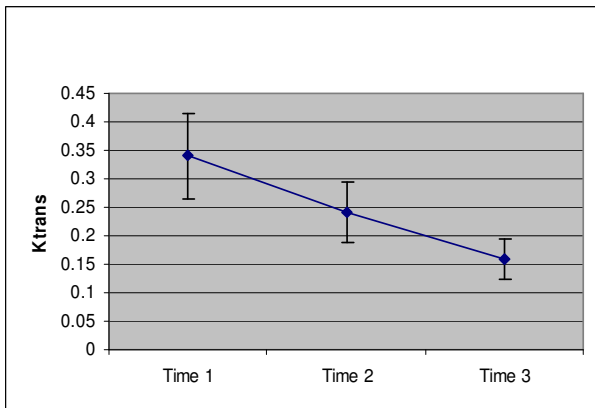


Figure 4: Trend line using manual plasma identification for subject 1. Note that the subject cannot be confidently classified as declining until time 3.

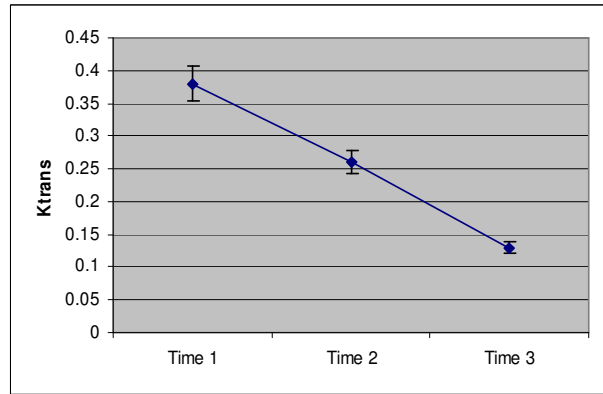


Figure 5: Trend line using automated plasma identification for Subject 1. This subject can be confidently classified as declining after time 2.

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