Parallel Observation of Left Ventricular Arterial Input Function and Brain Perfusion in Rats Using a Multi-Coil System

S. Pickup[1], S. Chawla[1], D-H. Kim[1], H. Poptani[1]
[1]Radiology, University of Pennsylvania, Philadelphia, PA, United States

Introduction

A wide variety of chemotherapy agents that target tumor hemodynamics are currently under investigation. The development of these agents will be greatly facilitated by the availability of non-invasive methods for accurately mapping tumor perfusion parameters in rodents . Dynamic contrast enhanced (DCE) MRI has been shown to provide such information in large animals and humans. Translation of these methods to small animals models has been hampered by low SNR, high heart rates in rodents and the need for very high temporal resolution. The authors have recently demonstrated a method for parallel observation of left ventricular (LV) arterial input function (AIF) and tumor perfusion in mice (1,2). However, this technique requires tumor implantation such that the core of the tumor is well visualized in a cardiac short axis image. The technique also requires use of a whole body coil for saturation of the entire blood pool in order to avoid inflow effects. The poor filling factor of the volume coil results in a low SNR for the target tissue.

In the present study, the limitations of the above mentioned techniques are addressed using a multi-coil approach. Receive only surface coils for the chest and target tissue, in this case a rat brain tumor, were used in combination with a whole body transmit coil. This apparatus allows for saturation of the entire blood pool while providing optimal SNR in the target tissues. It also allows study of orthotopically implanted tumors. The technique is demonstrated in rats bearing intra cranial 9L gliomas. The resulting data were fit to both the Tofts (3) and BOLus Enhanced Relaxation Overview (BOLERO) (4) models for tissue perfusion to yield maps of K^{trans}, v_e and τ (BOLERO only).

Methods

All MRI studies were performed on a 4.7T spectrometer (Varian Inc, Palo Alto, CA) equipped with a 12 cm I.D. gradient insert having a maximum amplitude of 25 gauss/cm. Tumor bearing Fisher rats (n=4) were prepared for imaging by induction of general anesthesia with 1% isoflorane in oxygen. A tail vein catheter was placed and loaded with a 20 mM solution of gadodiamide (GdDTPA-BMA; Omniscan, Amersham Health, Princeton, NJ). ECG and rectal temperature probes were placed and attached to a MR compatible vital signs monitoring system (SA Instruments, Stony Brook, NY). The animal was then mounted on the patient table (which also served as the support for the chest coil), the head coil was mounted and the entire apparatus was positioned in the volume coil. Following acquisition of scout images, T_1 maps of the brain and heart were acquired using a cardiac gated TOMROP protocol (5). Acquisition of seventy-five low resolution, cardiac gated, saturation recovery gradient echo images (TR = 2 heart cycles: ~ 320 msec, TE = 2.8 msec, matrix = 128x16, temporal resolution=5.3 sec) was then initiated. A 200 µl bolus of contrast agent was injected in 2 sec after acquisition of the 10'th image in the series. This study was followed immediately by acquisition of another 75 images using identical acquisition parameters except for the matrix, which was 128x32 (temporal resolution = 10.6 sec).

Images were analyzed off line using codes developed in the IDL programming environment (Research Systems Inc., Boulder, CO). The LV-AIF was extracted from the time series cardiac images by manually specifying an ROI representing the LV blood pool. The mean signal intensity in the ROI was then converted to contrast agent concentration using previously determined T_1 map and the literature values for the relaxivity (3.6 sec^{-1} $mmol^{-1}$ kg tissue water) and hematocrit (43%). A pixel wise non-linear least squares analysis was used to fit the observed signal in the brain and experimentally determined LV-AIF to the Tofts (3) and BOLERO (4) models of tissue perfusion. This analysis yielded maps of the tissue transfer constant (K^{trans}), the effective extra-vascular, extra-cellular volume fraction of water (v_e) and the mean lifetime of the intracellular water (τ).

Results

The multi-coil apparatus yielded high SNR images of both the brain and chest with no cross talk between the coils. The volume coil was shown to be effective in saturation of the entire blood pool. The mean T_1 values for normal grey matter and LV blood were 1.29±0.09 and 1.68±0.33 sec^{-1} which were consistent with previous studies at this field (5). The resolution of the dynamic images, though limited, was sufficient to resolve the structures of the brain and heart. The observed LV-AIF demonstrated a sharp increase of duration approximately equal to the injection time, followed by a multi-exponential decay, as observed earlier in mouse studies (1,2). Considerable inter-animal variability was observed in the AIF as noted previously (2).

The BOLERO model was consistently able to fit features of the signal profiles that could not be fit using the Tofts model. Typical parametric maps of K^{trans}, τ and v_e generated from the BOLERO analysis are depicted in Fig-1. Only pixels exhibiting a significant change in signal intensity following bolus administration were included in the analysis. This mechanism of thresholding eliminated most of the pixels in the normal brain due to the exclusion of contrast agent by the blood brain barrier.. Mean values for the perfusion parameters for all four animals over ROIs representing the entire tumor were K^{trans} = 0.023±0.013 sec^{-1}, τ = 1.30±0.57 sec and v_e = 0.52. The large standard deviations in the parameter values are due to the heterogeneity within the tumor as is evident in Fig-1. The K^{trans} and τ are elevated in the tumor rim while the v_e is elevated in the tumor core. This pattern was observed in three of the four animals studied. The tumor in the fourth animal was too small to resolve heterogeneity in the perfusion parameters.

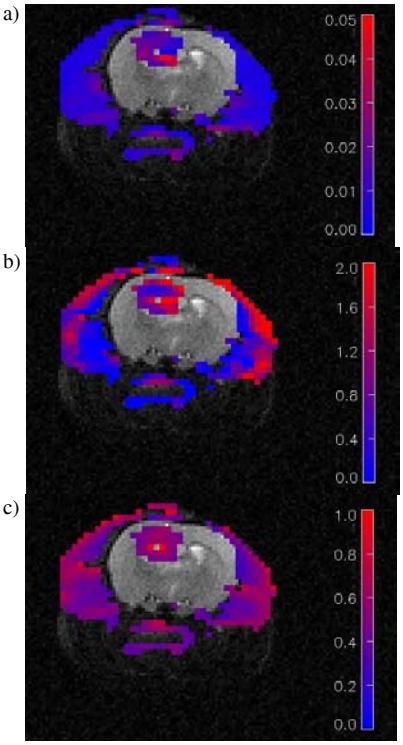

Figure 1. Parametric maps of K^{trans} (a), τ (b) and v_e are displayed on color scales super imposed on the T_2 weighted scout images of the brain. The color bars are in units of sec^{-1}, sec and a unit less ratio, respectively.

Conclusion

This study demonstrates the effectiveness of a multi-coil device in performing DCE-MRI studies of intra-cranial tumors in rats. The apparatus provides images with optimum SNR in the target tissue resulting in more reliable perfusion parameter estimates. The DCE data were analyzed using both the Tofts and BOLERO models and the BOLERO model was consistently able to fit features of the signal intensity profiles that could not be accounted for by the Tofts model. These observations support the thesis that water exchange between the intra and extra cellular spaces makes a significant contribution to tracer kinetics in small animal models.

References

1. Zhou; R.; Pickup; S.; Yankeelov; T. E.; Springer; C. S.; Glickson; J. D. *Magn Reson Med* **2004**, 52, 248-57.
2. Pickup; S.; Zhou; R.; Glickson; J. D. *Acad Radiol* **2003**, 10, 963-968.
3. Tofts; P. S. *J Magn Reson Imag* **1997**, 7, 91-101.
4. Yankeelov; T. E.; Rooney; W. D.; Springer; C. S. Proc. Intl. Soc. *Mag Reson Me*. **2002**, 10, 2114.
5. Pickup; S.; Wood; A. K. W.; Kundel; H. L. *Magn Reson Med* **2005**, 53, 35-40.