Separation of Intra- and Extra-Vascular Spaces in Human Brain with DCE-MRI and 11C- verapamil PET

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This DCE-MRI study was designed to attempt to provide an MR-based segmentation of the choroid plexus (CP) to allow correction of partial volume effects in PET studies with (R)-[C-11]-verapamil (VPM). VPM-PET imaging was used to examine P-glycoprotein (P-gp) function in the mesial temporal lobe (MTL) in patients with drug-resistant epilepsy and healthy controls (1). VPM-PET signal is high in CP and spills over into the hippocampus and other MTL structures. MR-based segmentation can, in theory, be used for partial volume correction but is hampered by the close relationship of CP and major blood vessels. We therefore tested several multi-compartment kinetic models designed to identify the intra- and extra-vascular spaces in human brain, including the extended Tofts model (ETM)(2), the kinetic models originated by Patlak (3), Brix (4) and Larson (5), using a commercially available software (Apollo Medical Imaging Technology Pty Ltd, Australia). We surprisingly found high values in the veins on K_{trans} maps for all these methods. The failure to separate K_{trans} from V_p is due to the well-known covariance (confounding) errors in the fitting procedure. Thus it was necessary to devise a new strategy, a "hybrid" approach, to reduce these errors (6). This approach extended the existing first pass model (EFPM) adaptively incorporating a two-compartment model. The purpose of this study was to assess the power of the new method in differentiating the intra- and extra-vascular spaces in human brain. 3D parametric maps of the transfer rate constant, K_{trans}, and plasma volume, V_p, were calculated for the whole brain using the new method, EFPM, as well as with the most commonly used traditional method, ETM. Mean K_{trans} and V_p in the regions of CP and great cerebral vein (GCV) were statistically compared to the traditional method for validation.

MATERIALS AND METHODS

Four healthy adults, 31-56 y, participated in the study. In addition to T1W, T2W volumetric morphological MR images, four consecutive 3D fast gradient recalled echo (GRE) images with an array of flip angles [2, 10, 20, 30]° were acquired for calculation of T1 maps of whole brain with an acquisition matrix size of 96 x 96 x 30. The 20° sequence was then repeated (n = 100) to produce a T1W dynamic series, the DCE-MRI, with a time resolution of Δt = 3.5 seconds and scan duration of 6.0 minutes. Contrast agent [0.1 mmol/kg of Gadoterate Meglumine (Dotarem, Geurbet S.A)] was given as an intravenous bolus injection over a period of 4 sec. Signal intensities, $S(t)$, of the DCE-MRI series were converted to voxel-wise curves of contrast agent concentration C(t); The EFPM used an optimized iteration scheme, based on Monte-Carlo simulation to the kinetic models, to generate 3D parametric maps of K_{trans} and V_p for the whole brain. In order to determine the improvement in separation of intra- and extravascular fractions, the ETM, which fits a standard Kety two-compartmental model to the DCE-MRI series, was also implemented and tested. Dynamic PET scans were acquired on the HRRT scanner for 60min following intravenous injection of 555 MBq VPM. The VPM-PET summation images were reconstructed using the ordinary Poisson-ordered subset expectation maximization and smoothed post-reconstruction with a 4 mm-width Gaussian function.

RESULTS

Figure 1 shows representative VPM-PET images as well as representative K_{trans} maps. Choroid plexus and pituitary gland show high radioactivity uptake on the PET images and high K_{trans} on maps derived using the ETM and EFPM. The GCV on the traditional ETM images shows high K_{trans} values, indicating its poor separation from intravascular components of the vessel. In contrast, the EFTM K_{trans} map shows much lower values from the vein. The new EFPM K_{trans} map is highly comparable to the VPM-PET image, where GCV shows low residual activity from VPM. Figure 2 shows one axial slice from the V_p maps from the same subject. The pattern of vessels on the EFPM V_p map is very similar to the ETM, although quantitatively different. Table 1 lists mean values of K_{trans}, V_p and fitting errors of CP and GCV for the two methods, the ETM and EFPM. P-values from 2-sided t-test are also listed. The new method significantly reduced the K_{trans} values in the veins (P = 0.003) but not in CP. In addition to the elimination of the measurement artifacts for K_{trans}, the new method significantly improved V_p measurements with 40% increases of measured V_p in GCV (P = 0.014). There was a trend towards lower fit errors in CP when the new method was used (P = 0.084). V_p in GCV was higher than in CP as expected for both ETM (P = 0.005) and EFPM (P = 0.001). A trend towards rectification of high K_{trans} values in GCV was found with the new method (P = 0.05). Classification test using the logistic regression further confirmed the improvement in separation between CP and surrounding veins. For the general model EFPM K_{trans} yielded 75% overall separation between two groups, and an AUC of 0.938. Both V_p estimated with both ETM and EFPM achieved 100% separation between two groups, and AUCs of 1.0.

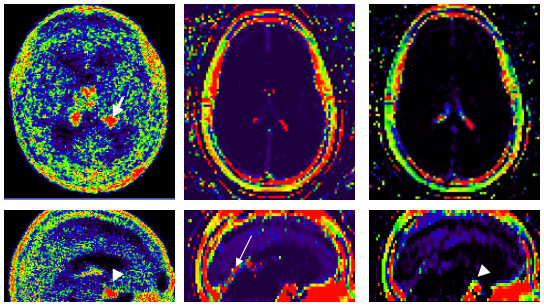

Figure 1. Axial (1st row) and sagittal (2nd row) planes of 3D images of VPM-PET (left), K_{trans} from ETM (middle), and EFPM (right). Choroid Plexus (thick arrow) and pituitary gland (arrow heads) are clearly depicted. The GCV shows high K_{trans} on the maps of ETM, rendered with red color, but not EFPM. Note that GCV and other large vessels were not found on the PET image render blue representing lowest intensity.

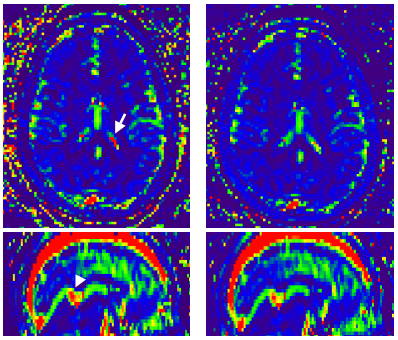

Figure 2. Axial (1st row) and sagittal (2nd row) planes of 3D images of V_p from ETM (left), and EFPM (right). Both ETM and DFPM images show choroid plexus (arrow) and GCV (arrow head) with high (red) and intermittent (green) Vp values, whereas blue color represents low values.

Table 1. Comparison between EFPM and ETM for kinetic parameters

	Fit Results*	EFPM	ETM	p-val
Choroid Plexus	K_{trans} (min^{-1})	0.003 ± 0.004	0.003 ± 0.004	0.980
	V_p (%)	0.06 ± 0.05	0.05 ± 0.03	0.165
	Error (%)	0.19 ± 0.07	0.25 ± 0.56	0.084
Great Cerebral Vein	K_{trans}(min^{-1})	0.001 ± 0.001	0.012 ± 0.011	0.0032
	V_p	0.13 ± 80.72	0.08 ± 0.05	0.0144
	error	0.15 ± 0.07	0.17 ± 0.08	0.570

CONCLUSIONS

The new DCE-MRI method using EFPM significantly improved differentiation between endothelial permeability (K_{trans}) and plasma volume (V_p). Excellent accordance was found between the 3D EFPM permeability maps from DCE-MRI and the 3D VPM-PET images. Strong separation between CP and surrounding veins has practical significance for partial volume correction of PET images (7). Good separation of K_{trans} and V_p will help understanding roles of CP in drug delivery. We expect that more accurate measurements of K_{trans} and V_p will improve characterization of lesions, where brain-blood barrier is disrupted and cerebral blood flow is disturbed.

REFERENCES

(1) Langer O et al, Epilepsia 2007; 48:1774; (2) Tofts PS et al, J. Magn Reson. Imaging 1999; 10:223-232; (3) Patlak CS et al, J Cereb Blood Flow Metab 1983; 3: 1-7; (4) Brix G et al, Radiology 1999; 210:269-276; (5) Larson KB et al, J Cereb Blood Flow Metab 1987; 7:443-463; (6) Li KL & Jackson A, MRM 2003; 50: 1286-1295; (7) Quarantelli M et al, J Nucl Med 45; 192-201.