Concurrent measurement of brain perfusion, blood volume and blood brain barrier permeability using dynamic contrast enhanced T_1 -weighted MRI

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Introduction: The measurement of brain perfusion (CBF) and cerebral blood volume (CBV) is important when diagnosing and treating vascular, degenerative and neoplastic diseases. These diseases are often associated with an increase of blood brain barrier (BBB) permeability. One clinical application relates to the discrimination between tumor recurrence and tissue degradation following radiation therapy. Despite the widespread use of MR perfusion imaging based on bolus tracking a concurrent estimation of CBF, CBV and permeability has proved difficult to achieve. Using dynamic contrast enhanced (DCE) MRI (1,2,3), an estimation of perfusion has not been possible and an estimation of the CBV has been problematic (4). In dynamic susceptibility contrast (DSC) MRI the effect of BBB leakage may compromise the estimation of CBV, partly due to a mixing effect of T_1 and T_2* relaxation (5). Generally, if CBV is estimated as the volume of distribution of the tracer an overestimation will occur in areas with BBB leakage. We present a methodology whereby a concurrent estimation of CBF, CBV and the permeability surface area (PS) product can be obtained. The method is based on DCE-MRI (6) and fundamental tracer kinetic principles. We demonstrate the method in patients with a brain tumor.

Theory: Basic tracer kinetic theory states that $C_t(t)$ = CBF $C_a(t) \otimes R(t)$ where $R(t)$ is the residue impulse response function and $C_t(t)$ and $C_a(t)$ are tissue and arterial concentration curves. This equation requires linearity only and is independent of the exact distribution of the tracer in the compartments. $R(t)$ and CBF can be determined using deconvolution. The mean transit time MTT is the time integral of $R(t)$, and the volume of distribution of the tracer V_d is calculated from the central volume principle as V_d=CBF MTT. If the BBB is intact, V_d should represent the cerebral blood volume. If leakage occurs then we expect V_d to become larger than the CBV as accessible extravascular compartments are included. The BBB permeability and vascular volume can be estimated independently using Patlaks method (7). Here the tissue is modelled as a reversibly accessible (blood) compartment, and an irreversibly accessible (extravascular) compartment. If plotting $C_t(t)/C_a(t)$ as a function of $\int_0^t C_a(\tau)d\tau/C_a(t)$ the slope represents the unidirectional influx constant (K_i), and the intercept represents the volume of the vascular compartment (denoted V_b). For a low permeating tracer, K_i approximates the *PS* product.

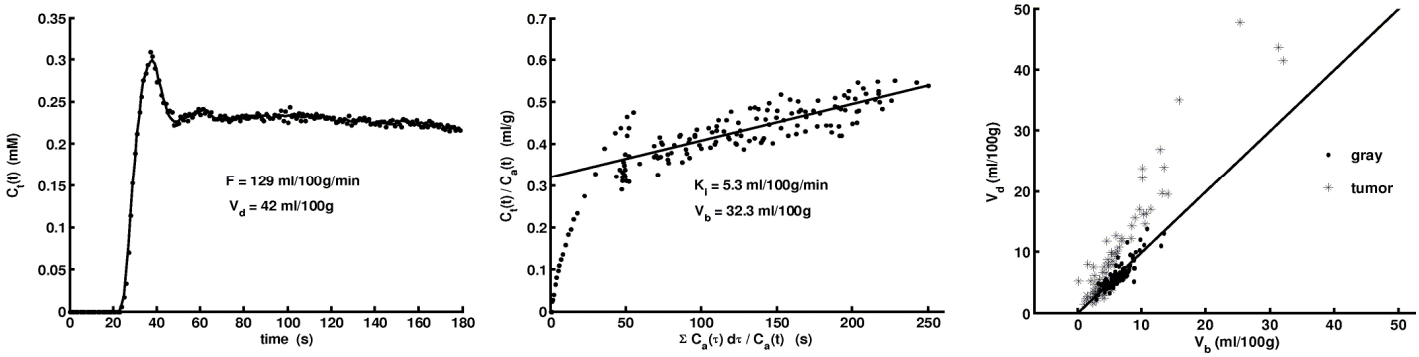

Fig. 1. (a), (b) shows data (dots) from a ROI placed in a tumor. (a) shows fit (line) based on deconvolution of a concentration-time curve, while (b) is a Patlak plot with a fit (line) to the linear part. (c) shows V_d as a function of V_b for all ROIs. The line of identity is also shown.

Methods: Ten patients with a primary brain tumour underwent perfusion imaging. MRI was performed on a 3 T Philips Achieva (Philips Healthcare, The Netherlands) equipped with an eight-element receive head coil. A T_1 measurement and the bolus tracking utilized a saturation recovery gradient echo sequence. Dynamic image parameters were: saturation delay 120 ms, flip angle 30°, TR=3.9 ms, TE=1.9 ms, centric phase ordering, SENSE factor 2, matrix 96×61 (reconstructed to 256×256), FOV 230×182 mm^2, 4 slices, slice thickness 8 mm, dynamic image time 1.0 s, 180 frames. In order to obtain an AIF with minimal partial volume, the most caudal slice was placed orthogonal to either the left or right internal carotid artery (ICA). The Gd bolus (Magnevist; 0.05 mmol/kg bodyweight) was injected after the 10th frame. The voxel in the ICA with maximal signal during the bolus passage was first chosen for the arterial input function. CBF and V_d were quantified by model-free deconvolution using Tikhonov regularization (as in (6)). V_b and K_i were determined from the Patlak plot. For all patients, on each slice through a tumor, 4-8 ROIs were placed in enhancing and non-enhancing areas. In addition, 4-8 ROIs were placed in non-affected gray matter and 2-3 ROIs were placed in non-affected white matter.

Results: Perfusion in gray and white matter was 72±16 and 31±8 ml/100g/min, respectively, and 56±45 ml/100g/min in tumors. The corresponding values for CBV were 6±2, 4±1, and 7±6 ml/100g, and the PS products were 0.9±0.4, 0.9±0.3 and 2.2±2.1 ml/100g/min. Fig. 1 shows examples of parameter estimation using deconvolution (a) and the Patlak plot (b). Remark the overestimation of blood volume in (a) compared to (b). In (c) we compare the two estimates of CBV, V_b and V_d. They agree for normal gray matter, whereas V_d tends to be larger in tumor tissue. Finally, Fig. 2 shows maps of CBF, K_i, V_d and V_b for a tumor patient with a large glioblastom.

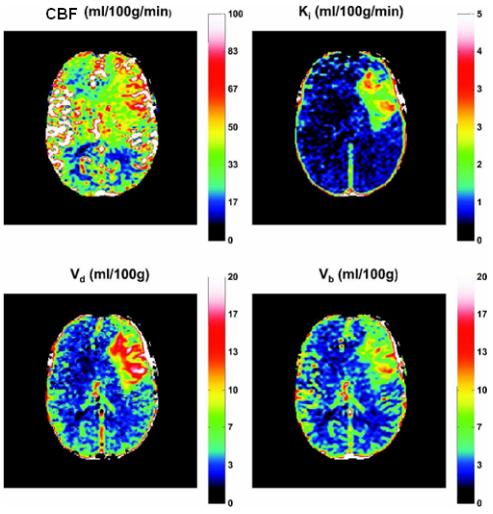

Fig. 2. We show maps of F, K_i, V_d and V_b for a tumor patient with a large glioblastom. Note that the values of V_d are higher that V_b in the area with a deficient BBB.

Discussion: The present study shows that it is possible to estimate perfusion, blood volume and permeability from a single bolus injection, even in cases with a deficient BBB, when using T_1-weighted DCE-MRI. Our results point to the importance of considering the effect of leakage on the CBV estimation. We addressed this by explicitly including the extravascular compartment in the tracer kinetic modelling. The methodology shown here can be applied to determine both CBV and BBB permeability in tumor patients. This study is to our knowledge the first to report on the permeability of the normal BBB for a Gd containing contrast agent. Unexpectedly, K_i was consistently found to be larger than zero. This issue needs to be studied further.

References: (1) Larsson H, et al., MRM 16:117 (1990); (2) Tofts PS, et al., MRM 17:357 (1991); (3) Tofts PS, et al., JMRI 10:223 (1999); (4) Johnson G, et al., MRM 51:961 (2004); (5) Boxerman JL, et al., AJNR 27:859 (2006); (6) Larsson H, et al., JMRI 27:754 (2008); (7) Patlak CS, et al., JCBFM 5:584 (1985)