A dynamic contrast enhanced MRI protocol optimised to the concentration ranges of P792 detected in the vascular input function and tumour.

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Introduction: Dynamic contrast enhanced magnetic resonance imaging (DCEMRI) presents as a method applicable in both man and pre-clinical investigations to measure haemodynamic components of normal and pathological tissue. P792[1] ('Vistarem', Guerbet, Paris) is a gadolinium chelated macro-molecular (6.47 kDa) rapid clearance blood pool agent (RCBPA) currently in Phase III trials which can provide haemodynamic information associated with tumour blood flow per volume tissue F/V_t (ml. sec^{-1}. ml^{-1}), fractional plasma volume νp (%) and permeability surface area product PSρ (sec^{-1})[2]. Nevertheless, the total functional vascular volume of the tumour is small and consequently the signal obtained on administering a RCBPA is much reduced compared to a non-specific agent such as Gd-DTPA that rapidly diffuses into the interstitial space[3]. In contrast, when simultaneously obtaining a vascular input function (VIF) from a major vessel the contrast agent concentration is very large. Consequently, the DCEMRI protocol needs to be capable of measuring the divergent concentrations of the tumour and a major blood vessel. In practice, this can only be achieved using compromised experimental parameters that reduce the sensitivity of the technique toward tumour contrast agent concentrations in order to adequately monitor VIF from a major blood vessel. In this study we describe a DCEMRI modified keyhole[4] spoiled gradient echo (SPGR) experiment. This has been optimised for the detection of both tumour and blood pool contrast agent concentration permitting the quantitation of 1) the uptake of small concentration of P792 and 2) the haemodynamic parameters (F/V_t, νp and PSρ) of a subcutaneously implanted colorectal human tumor (SW620) xenograft rat model.

Methods: **Optimisation of DCEMRI**: As seen in Fig.1 a modified keyhole SPGR experiment would be more sensitive to the low P792 concentrations, [P792], detected in tumours if a small excitation flip angle was used. However, the use of small flip angle also reduces the range of concentrations for which the MRI signal is increasing, making it impossible to use for the large concentrations seen in major blood vessels.. In this study we have overcome this limitation by adding a saturation band to the modified keyhole SPGR sequence and applying it across the blood vessel used to measure the VIF. Using this approach the signal intensity associated with the concentration range in the VIF is always increasing (Fig.2) and high sensitivity toward the low concentration detected in the tumour is maintained. This technique was tested on a colorectal human tumour (SW620) xenograft rat model. **Animal experimentation** : SW620 tumours were implanted dorsally in the athymic rat (n=3) and allowed to grow for ~ 10 days. Animals were anaesthetised and placed in a custom built Perspex lidded bed. A tail vein was catheterised for i.v. administration of P792 (0.0045mmol/kg body weight) and the lid, accompanied by a carriage of P792 calibration agar gels, was placed over the animal. Imaging was performed at 4.7T (Varian, Palo Alto, CA) using a 6 cm diameter birdcage resonator. A T2 weighted coronal scan was used to plan a DCEMRI slice through the tumour and left ventricle. DCEMRI data was acquired for 5 min (TR /TE 0.013 /2.3ms, $\alpha = 15°$, FoV 6cm, SlThk 5mm, sagittal saturation band ~ 20mm across left ventricle, temporal resolution of 0.5s/image), during which time P792 was administered. A single slice image was then acquired through the tubes with and without a FoV saturation band for the VIF and tumour [P792] calibration curves. Signal was measured over each gel in the carriage and two calibration curves generated (Fig. 2). The mean SI time course in ROI's placed at the centre of the left ventricle lumen and over the tumour was extracted from the dynamic series. The SI for the VIF and tumour was then converted to P792 concentration over time, [P792](t), using the two equations corresponding to $M=M_0.\sin\alpha.\exp(-TE/T_2^*).(1-\exp(-TR/T_1))$ and $M=M_0.\sin\alpha.\exp(-TE/T_2^*).(1-\exp(-TR/T_1)/1-\cos\alpha.(\exp(-TR/T_1)))$, respectively. The resulting [P792](t) data were analysed using a monodirectional bicompartmental tumour kinetic model (1) in order to resolve F/V_t, νp and PSρ.

Results: Fig. 3 shows the MR image through the upper chest of the athymic rat with and without the saturation band. The saturation band is applied across the left ventricle to achieve a signal change associated with [P792](t) that could be calibrated simultaneously along with the small [P792](t) observed in the tumour. The [P792](t) is plotted from the left ventricle and tumour (Fig. 5 & 6). These data were then inserted into the monodirectional bicompartmental tumour kinetic model in order to resolve F/V_t, νp and PSρ; illustrative values for the tumors converged around 0.022 ± 0.0042 ml/sec/ml, 2.12 ± 0.78 %, and $0.0002 \pm 6.35\text{x}10^{-5} s^{-1}$ (mean ± SD). F/V_t and PSρ are higher than previously reported although a different tumour line was used in this case (PC-3)[1].

Fig.1

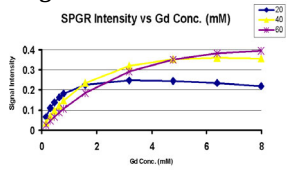


Fig.2

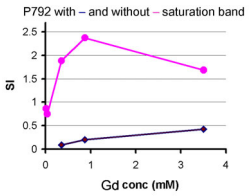


Fig.3

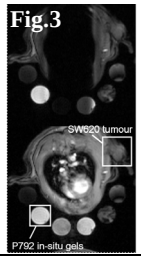


Fig. 4

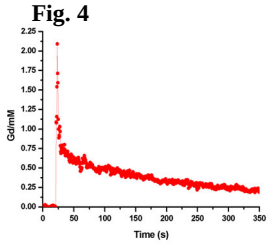
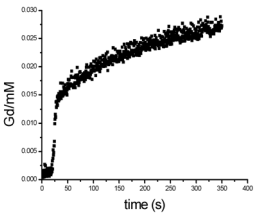


Fig.5



Discussion: In the present investigation the measurement of concentration changes of a macro-molecular RCBPA (P792) in both left ventricle and tumour was achieved in athymic rats by applying a selective saturation band across the left ventricle and using a modified keyhole SPGR sequence with a low flip angle in order to increase the sensitivity to the small [P792] changes observed in the tumour. The saturation band nulled any signal from the blood in the left ventricle and permitted a high quality VIF to be detected when P792 was administered. With the increased sensitivity achieved using this method the haemodynamic parameters (blood flow, blood volume and vascular permeability) of a human tumour xenograft was successfully obtained.

[1] Port M *et al*., MAGMA 12 121-127 2001

[2] Pradel *et al*., MRI 21(8):845-51 (2003)

[2] Su *et al*., MRM 39 259-269 (1998)

[4] Gao J-H, et al., MRM. 35:854-860 (1996).