Quantitative perfusion imaging by USPIO bolustracking: the Maximum Slope Model

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Introduction Assessment of brain perfusion by absolute quantification of cerebral blood flow (CBF), cerebral blood volume (CBV), time of arrival (TA) and time-to-peak (TTP) critically contributes to the accuracy of characterizing tissue status, predicting lesion outcome, as well as monitoring therapy in clinical and experimental stroke studies[1].Often, dynamic susceptibility contrast-enhanced (DSC-) (bolus tracking) MRI is used to monitor the arrival and passage of an intravenously injected bolus of Gd-DTPA in brain tissue, which enables estimation of perfusion parameters by deconvolution[2]. In this work we investigated the use of ultrasmall particles of iron oxide (USPIO) for perfusion imaging, which would enable the simultaneous assessment of (changes in) vascular architecture (e.g. angiogenesis) by probing microvessel density and vessel size with steady-state contrast enhanced (ssCE-)MRI[3]. For ssCE-MRI, USPIO are particularly suitable due to their strong susceptibility effect and long blood half-life as compared to Gd-based contrast agents. However, the stable intravascular contrast agent concentration at the same time induces a different signal decay time course, preventing the signal to return to baseline after first passage. This may complicate estimation of tissue perfusion parameters using a deconvolution approach. Therefore we propose an alternative method for absolute quantification of tissue perfusion by USPIO bolus tracking, which is known from CT perfusion imaging[4] as the maximum slope model (MS).

Methods The MS model assumes that the maximum slope of the contrast agent concentration curve is reached before venous outflow starts[5]. T_1 effects due to USPIO are ignored, since no instantaneous USPIO extravasation is expected. *Cerebral blood volume:* The change of tissue $R_2^*[s^{-1}]$ can be described in terms of the echo time (TE) and the MR signal before (S_{pre}) and after (S_{post}) administration of USPIO (Eq.[1]). In conjunction with the tissue relaxivity induced by intravascular USPIO, $r_{2\ t,USPIO}^*$ in $[s^{-1}/M]$, the tissue concentration (C_t [M]) can be determined (Eq. [2]), which enables estimation of the fractional blood volume (fBV), assuming the vascular Fe concentration (C_{vasc} [M]) is known [Eq. 3]. The latter can be estimated from the susceptibility difference between vasculature and tissue ($\Delta\chi_{vasc}$[ppm]) and the USPIO volume susceptibility χ_v in [ppm/M] [Eq. 4]. $\Delta\chi_{vasc}$ and χ_v can be estimated *in vitro* by analyzing blood samples and an USPIO dilution series, respectively. Using these values and Eqs. [2-5], $r_{2\ t,USPIO}^*$ can be determined (Eq. [6]).

$\Delta R_{2\ t}^* = \ln(S_{pre}/S_{post})/TE$ [1] $\quad C_t = \Delta R_{2\ t}^* / r_{2\ t,USPIO}^*$ [2]

$C_t = C_{vasc} \cdot fBV$ [3] $\quad C_{vasc} = \Delta\chi_{vasc}/\chi_v$ [4]

$\Delta R_{2\ t}^* = (\gamma \cdot \Delta\chi_{vasc} \cdot B_0 \cdot fBV)/3$ (SI units) [5] $\quad r_{2\ t,USPIO}^* [s^{-1}M^{-1}] = (\gamma \cdot \chi_v B_0)/3$ [6]

Cerebral blood flow: The MS model describes flow (F [ml/s]) per unit volume (V [ml]) as the maximum slope of the tissue concentration curve divided by the maximum vascular concentration (Eq. [7]). The maximum vascular concentration, $C_{vasc,max}$, can be determined using $r_{2\ t,USPIO}^*$, fBV and the maximum change of the tissue relaxation rate, $\Delta R_{2\ t,max}^*$, as described in Eq. [8]:

$F/V = \max(dC_t(t)/dt)/\max(C_{vasc,max}(t))$ [7] $\quad C_{vasc,max} = \Delta R_{2\ t,max}^* / (r_{2\ t,USPIO}^* \cdot fBV)$ [8]

In vitro experiments: χ_v of USPIO (P904, Guerbet, France) was determined by analyzing a dilution series ranging from 0.08 to 10mM Fe using a multiple GRE sequence (TR/TE/dTE=5000/2.5/2.5 ms), with $\Delta\chi=3\varphi/(\gamma B_0 TE)$ for parallel oriented sample tubes. $\Delta\chi_{vasc}$ was estimated by analyzing the susceptibility difference of serum ($\Delta\chi_s$) of blood samples taken pre- and post-contrast (t_{post}) agent injection, in conjunction with its hematocrit (Hct), which was determined at 10.000 RPM for 5 min, and the P904 blood half-life in rats, $T_{1/2}$, was estimated image-based to be 197 min. Then $\Delta\chi_{vasc}(t_{bolus}) = \Delta\chi_s(1\text{-}Hct)\cdot\exp(-t_{post}/T_{1/2}/\ln(2))$.

In vivo experiments: Quantitative perfusion imaging was performed in five rats (Wistar, 320-360g) two weeks after 45 min transient unilateral middle cerebral artery (MCA) occlusion. Normal CBV and CBF values were determined contralaterally in normal appearing gray (caudate putamen (cpu) and cortex (cx)) and white matter (corpus callosum (cc)). A fast single shot GRE-EPI sequence was used for bolus tracking. Imaging parameters: TR/TE=300/25ms; 500 dynamic scans; scanmatrix: 64^2, reconstructed to 128^2; FOV = 32x32 mm, 5 slices of 1 mm. A bolus of 5.6 mg Fe/kg, ~200 mM (0.5 µl/g body weight (bw)) was injected intravenously.

Processing: The maximum slope of the tissue concentration curve ($\max(dC_t(t)/dt)$) was determined by linear fitting, using a 3 point-sliding window, starting at a significant signal change with respect to baseline.

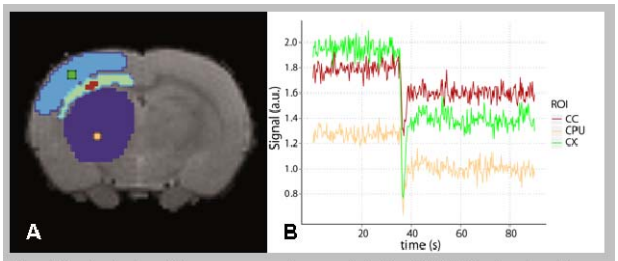

Fig. 1 Typical signal time course observed during USPIO bolus tracking in cortex (cx), caudate putamen (cpu) and corpus callosum (cc)

Results χ_v of USPIO was determined to be 1.25 ppm/mM, tissue relaxivity due to intravascular USPIO $r_{2\ t,USPIO}^* = 0.53$ MHz/M, and Hct = 42.2 ± 2.2 (mean±sd). Average C_{vasc} and $\Delta\chi_{vasc}$ directly after bolus tracking, based on serum measurements which were corrected for Hct and estimated blood half-life, were 1.9 mM and 2.4 ppm (in SI units), respectively. Fig. 1. shows typical signal patterns observed during USPIO bolus tracking, clearly demonstrating that the signal does not return to baseline after first passage. Fig. 2 displays maps of absolute CBF (a) and CBV (fBV) (b) of 3 coronal slices, scaled to 0-175 ml/100g/min and 0-4%, respectively. The highest values of both CBF and CBV can be found in cortical and subcortical gray matter regions, whereas the lowest CBF and CBV are shown in white matter. This was confirmed by ROI analysis, which revealed average fBV values of 0.7±0.1%, 1.4±0.3% and 2.5±0.5% and CBF values of 45±8, 71±16 and 119±33 ml/100g/min in cc, cpu and cx, respectively.

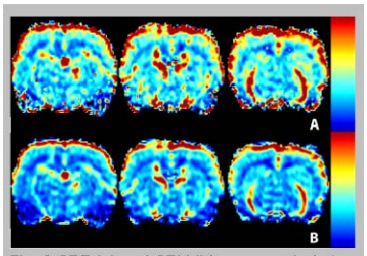

Fig. 2 CBF (a) and CBV (b) maps scaled at 0-175 ml/100g/min and 0-4% respectively

Discussion This work demonstrates the potential of the maximum slope model to enable quantitative perfusion imaging based on USPIO bolus tracking. The MS model has been applied successfully to estimate absolute CBV and CBF values in rats *in vivo*, providing realistic perfusion measures. Highest values of both CBV and CBF were found on the brain surface (dorsal superficial cerebral arteries), which corresponds with the high vascular density in this area[6]. Furthermore, the CBF ratio between gray and white matter varied between 2 and 3, which agrees with findings from the literature.

The simplicity of the MS model, as compared to the more complex deconvolution models, renders it an attractive alternative, since it 1) is independent of an arterial input function, 2) applies to a regime with residue function R(t)=1, 3) is independent of timing delays, 4) is insensitive to recirculation, and 5) does not need calibration by other modalities to provide absolute CBF and CBV values. The latter is possible since a) the proportionality constant needed, often referred to as k but in the present work as $r_{2\ t,USPIO}^*$, is determined based on the χ_v of USPIO, and b) USPIO have a long blood half-life, which enables estimation of the steady state vascular concentration based on the total blood volume and the injected bolus volume. A downside of the MS model may be that its main assumption, the fact that the maximum slope should be reached before venous outflow starts, may be violated in specific cases, which would lead to an underestimation of CBF. Challenging cases include low flow regions as well as tissue perfused by collateral flow. However, these regions are also problematic when analyzed with the deconvolution approach, as well as with a recently proposed method strongly resembling the MS model, referred to as 'early time points perfusion imaging'[7]. Further research needs to be done to investigate the accuracy and reproducibility of the MS model in estimating perfusion in these challenging situations.

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