Vessel Size Imaging with iron oxide and with gadolinium: a comparative study in rodent

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Introduction

Blood Volume fraction (BVf) and Vessel Size Index (VSI) MR imaging are powerful tools for characterizing tumor microvasculature and its evolution under therapy. BVf and VSI imaging are based on the measurement of the changes in R_2 (ΔR_2) and in R_2* (ΔR_2*) induced by a contrast agent (CA) [1]. In brief, two types of CA have been evaluated: iron oxide particles (USPIO), in animals, and Gd chelates (Gd), in humans [2,5]. Due to the difference in magnetic susceptibility between the two CA, experiments have been performed at steady-state for USPIO (i.e. imaging before and after USPIO injection) and during the first passage of Gd (ΔR_2 and ΔR_2* are measured at bolus peak). In this study, we compare VSI values obtained with dynamic and steady-state acquisition schemes with each CA in rats bearing C6 glioma.

Material and Methods

Experiments were performed at 4.7T (Bruker Avance III system) using volume/surface cross coil configuration. Wistar rats (n=11), bearing an intracerebral C6 glioma (15 days and 17 days of growth) were anaesthetized using isoflurane (2%) and their tail vein was equipped with a catheter for CA injection.

MRI protocol: T_2w imaging for anatomy, EPI with both gradient and spin-echoes (TR=500ms, GE=12 ms, SE=60ms, FOV=3x3cm², matrix=64x64, 2mm-thick) to monitor the 1st passage of Gd-bolus (Gd-DOTA, 200µmol/kg), 3 minutes later, same EPI sequence to monitor the 1st passage of a second injection of Gd to mimic the case of Gd-loaded tumor [4,5]. Four hours later, the same animal was imaged as follows: GE-based apparent diffusion coefficient (ADC) mapping, EPI-based ADC mapping, MGESE (TR=6s, 8 GE=[3-35] ms, SE=60 ms, FOV=3x3cm², matrix=64x64, 2mm-thick), EPI (same parameters as for Gd) to monitor the 1st passage of USPIO bolus (Sinerem®/Combidex®, Guerbet/AMAG Pharmaceuticals, 100µmol Fe/kg (half dose to avoid complete signal destruction)), and MGESE again after a second injection of USPIO (100µmol Fe/kg) to reach a total of 200µmol Fe/kg, the amount that has been used in steady-state approaches for measuring VSI [1].

Data processing was performed on Matlab using home-made software:

- $VSI_{USPIO,MGESE}$ was computed from the MGESE data (using 0.28 10^{-6} cgs for the change in magnetic susceptibility ($\Delta\chi$) induced by USPIO). This map was arbitrarily taken as reference for this study.
- $VSI_{Gd,Peak}$: The two bolus curves derived from the EPI double-echo data were fitted pixel-wise with a gamma-variate function taking into account the dilution of the CA [2] and using a non linear fit algorithm. $VSI_{Gd,Peak}$ was obtained from the ratio ΔR_2*/ΔR_2 which both were evaluated at the bolus peak concentration, for the gradient echo and the spin echo respectively. At bolus peak, $\Delta\chi$ is the highest and the static dephasing regime is achieved [2].
- $VSI_{Gd\ loaded,Peak}$ was computed as $VSI_{Gd,Peak}$ but using EPI double-echo data collected during the second bolus of Gd (case of the Gd-loaded tumor).
- $VSI_{USPIO,Peak}$ was determined as $VSI_{Gd,Peak}$ but using the EPI double-echo data collected during the USPIO bolus passage.
- $VSI_{USPIO,SS}$ was determined using ΔR_2* and ΔR_2 computed from the arithmetic means of the double-echo EPI signals acquired before (baseline signals, 25 images) and after (40 images) the first passage of the USPIO bolus.

To quantify VSI with each method, the peak concentration for Gd was set to 5 mmol/L and that of USPIO to 2.5 mmol/L (data from the laboratory). Two regions of interest were eventually defined: the whole tumor and the contralateral striatum, for each slice of interest. Every pixel with a VSI value over 50µm was excluded (value outside the range of validity [1]).

Results

Representative VSI maps obtained in this study are shown in Fig 1. Red pixels correspond to rejected values. The correlation between VSI estimates with each method and with the reference method ($VSI_{USPIO,MGESE}$) are presented in Fig. 2. Absolute VSI values are consistent with previous studies using MGESE sequence [3]. USPIO SS and Gd peak methods seem to correlate with MGESE method ($R^2 > 0.72$) with a slope smaller than 1. Gd-loaded data are not in good agreement with MGESE data ($R \approx 0.469$). This suggests that the presence of Gd outside the C6 microvessels may alter ΔR_2 and ΔR_2* in different ways.

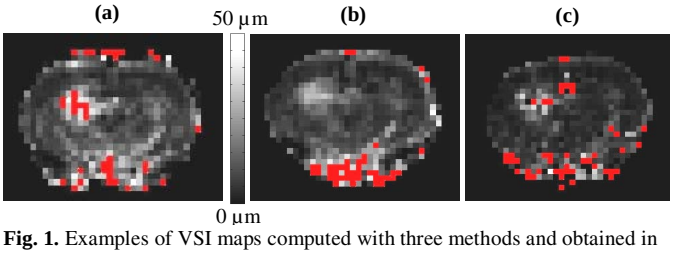

Fig. 1. Examples of VSI maps computed with three methods and obtained in the same animal. **(a)** MGESE **(b)** Uspio SS **(c)** Gd Peak.

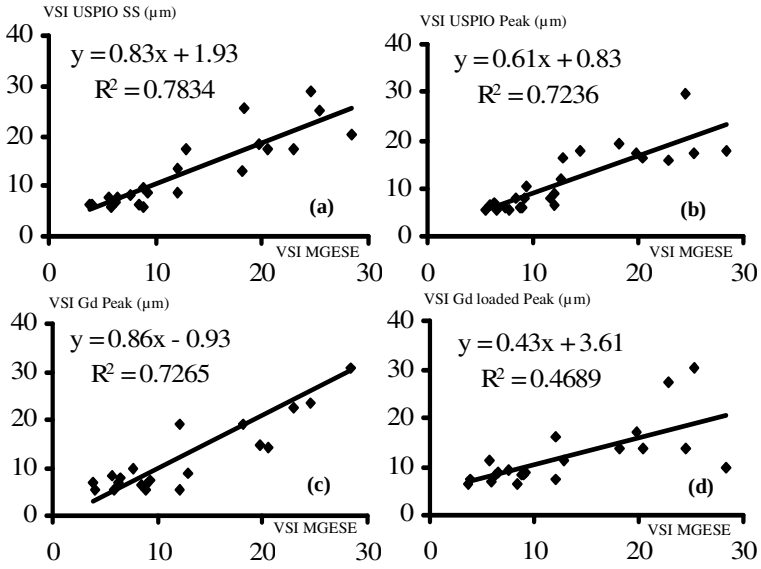

Fig. 2. VSI values in µm obtained using double-echo EPI (y-axis) and MGESE (x-axis) sequences. Each point corresponds to a ROI (either contralateral or tumor) in a single animal. The black line corresponds to the linear fit through the data. **(a)**. Uspio SS *vs* USPIO MGESE. **(b)** USPIO Peak *vs* USPIO MGESE. **(c)** Gd Peak *vs* USPIO MGESE **(d)** Gd loaded Peak *vs* USPIO MGESE.

Conclusion

This study shows that Gd-based and USPIO-based estimates of VSI are well correlated in healthy brain and for this tumor model. Loading a tumor with Gd appears in this study to alter the VSI estimates. Peak CA concentration – difficult to assess in vivo – remains however a key parameter to obtain quantitative VSI estimates. The error on peak CA concentration may have contributed to the smaller VSI values obtained with the EPI-based methods. This study indicates that, despite the low magnetic susceptibility of Gd, relative VSI measurements using Gd (without tumor pre-loading) appears to be a well suited technique to follow-up tumor microvasculature in humans for whom USPIO are not currently approved [4,5].

References

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