Steady-State Quantification of ΔR_2 (SSTAR2) with Combidex for Measuring Cerebral Blood Volume

J. F. Dunn[1,2], D. A. Kelly[1,2], C. R. McCreary[1,2], R. Tyson[3], D. Kirk[2], T. Foniok[3]

[1]Radiology, University of Calgary, Calgary, AB, Canada, [2]Experimental Imaging Centre, University of Calgary, Calgary, AB, Canada, [3]Institute for Biodiagnostics (West), National Research Council, Calgary, AB, Canada

INTRODUCTION

We showed it is possible to use a super paramagnetic iron oxide or SPIO (MION) to obtain repeated measurements of cerebral blood volume (CBV) [1]. The MR imaging method, Steady-STAte quantification of ΔR_2 ($SSTAR_2$), involves quantification of R_2 before and after infusion of contrast. The change in R_2 with contrast is differentially sensitive to the microvasculature [2]. This method should be useful to quantify angiogenesis in the same animal on different days and allow for the collection of high-resolution images [1]. The current study follows the first by comparing single and multi-exponential analysis and uses Combidex, which is under active commercialization. The study also uses higher field strength and includes data on the echo time dependence.

METHODS

MR imaging on Wistar rats was conducted at 9.4T using a Bruker console and a 35 and 45mm quadrature birdcage coil. A multi-echo spin echo sequence was used to quantify R_2 *in vivo* (TR=1.5s, TE=varied from 3-15ms, 128-24 echoes respectively, FOV=3x3 cm, matrix=128x128 pixels, slice=1.5 mm, NT=4). The *in vivo* calibration was done by sequentially infusing Combidex® (Advanced Magnetics, MA). Multi-echo spin echo (SE) images were obtained before and after infusion. Blood samples were taken for hematocrit (Hct) and to quantify serum R_2 using the same parameters as were used *in vivo* after a 10 fold dilution with saline. In long studies, corrections were made for the loss of contrast due to the ½ life of 120 minutes (pers. comm., Dr. Jacobs, Advanced Magnetics). CBV was calculated as $\Delta R_2 t/\Delta R_2 b$, where Δ=the difference in R_2 before and after contrast, t=cortical tissue and b=blood. Blood values are calculated from serum(s) and Hct using $\Delta R_2 b = \Delta R_2 s \cdot (1\text{-Hct})$.

RESULTS

The *in vitro* and *in vivo* calibration curves are linear over the ranges measured. The single exponential analysis and the multi-exponential analysis (non-negative least squares or NNLS) [5] measurements are summarized in Table 1 for echo times of 3 and 8ms. The CBV was calculated for single exponential at both echo times, but the NNLS analysis was only done for the 3ms data. This was because the NNLS analysis did not provide consistent results with the 8ms echo time data.

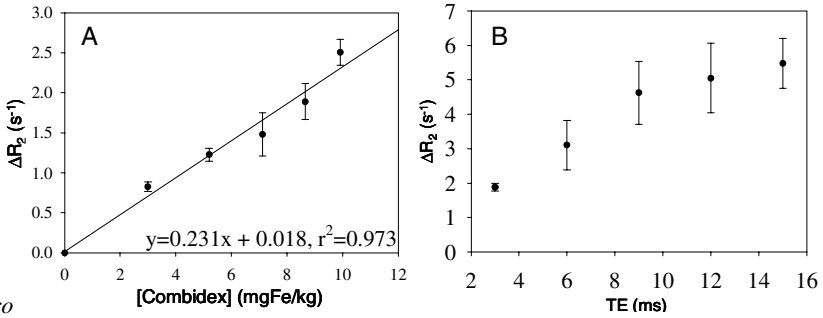

Figure 1: Calibration of relaxivity using a single exponential analysis: A) *In vivo* (mean±SD, n=3). An *in vitro* curve was also linear with a slope of $1660 s^{-1}*(mg/kg)^{-1}$; and B) Echo time dependence showing increased sensitivity with increased inter-echo time. The ΔR_2 was calculated after collecting multi-echo data with differing inter-echo spacing before and after infusion of 10mg/kg Combidex (mean±SD, n=3).

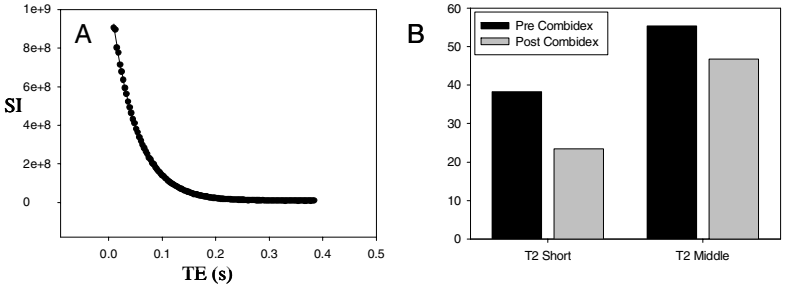

Figure 2: Example multi-exponential analysis: A) Decay function; and B) Example changes in T2 with Combidex. Analysis was done using NNLS with a maximum T2 of 1700 and 1000 components, TE=3ms and 128 echoes. All components shortened with Combidex.

Table 1: ΔR_2 (s^{-1}) and measured CBV with TE=3 and TE=8 (mean ±SD (n).

TE	ΔR_2 Single Exponential	ΔR_2 NNLS mid R_2	ΔR_2 Serum	CBV %v/v Single Exponential	CBV %v/v NNLS
3ms	2.1± 0.4 (9)	4.9±3.9 (6)	135±33 (6)	1.8±0.7 (6)	4.7±3.5 (6)
8ms	3.4±0.7 (4)	Insufficient points	124±35 (2)	2.9±0.4 (2)	

DISCUSSION

The sensitivity of the *in vivo* calibration was approximately 1/3 of MION, which was likely due to differences in collection parameters [1]. The previous study used a longer echo spacing (8-10ms) which increases sensitivity (Fig. 1B) but decreases the specificity to the capillaries [4]. The CBV values at 3ms, measured with a single-exponential are similar to the 2.1% measured with radiotracers [3]. ΔR_2 measured with NNLS was larger and had greater variation (Table 1, Fig. 2). The coefficient of variation (CV) was 20% with single exponential and 80% with NNLS analysis (Table 1). The increased variation is likely because the large number of fittings used reduces precision. Although NNLS provides a multi-component analysis, it is unlikely to improve sensitivity in measurements of CBV. There was little difference in CV with different echo times (Table 1), indicating that reduction in ΔR_2 did not sacrifice the capacity to detect differences in CBV and that CBV can be measured with a precision of ±20%.

REFERENCES

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