Pharmacological MRI in mice with the Rapid Steady State T_1-technique and intraperitoneal contrast agent administration

Teodora-Adriana Perles-Barbacaru[1], Francois Berger[1], and Hana Lahrech[1]
[1]*Grenoble Institute of Neurosciences, INSERM U836, Grenoble, France*

Introduction: Noninvasive quantification of regional cerebral blood volume fraction (BVf) by magnetic resonance imaging (MRI) is not only useful for tumor classification and grading [1], but also to study the vasoreactivity to pharmacological challenges or the neuroactivity to sensory stimuli via the mechanism of neuro-vascular coupling [2,3].
MRI approaches that require intravenous (i.v.) injections of contrast agents [2,3,4] pose limitations for mapping the cerebral BVf in small animal models such as mice because of the difficulty to gain repeated i.v. access, and because their rapid hemodynamics and small brain size result in low signal to noise ratio [5]. We recently demonstrated [6] that the Rapid Steady State T_1 ($RSST_1$) MRI technique, previously used with i.v. injections [4] in rats, can be used with intraperitoneal (i.p.) injections of Gd-DOTA to safely and reliably acquire cerebral BVf maps in mice. In addition, this administration route increases the time window for cerebral BVf measurement from a few seconds to at least 20 minutes in most brain regions [6]. In this study, we used this time window to study the sensitivity of the $RSST_1$-technique to vasodilation in a pharmacological MRI experiment.

Material and methods: All animal experiments were approved by the institutional ethic committee and performed in a 47/40 Bruker Biospec USR AV III scanner with a homogenous coil for transmission and a mouse head surface coil for reception.
Vasodilation was induced pharmacologically in NMRI mice (n = 7) using Acetazolamide (Diamox, a carbonic anhydrase inhibitor). They were equipped with two i.p. catheters (24G) connected to extension lines preloaded with 6 mmol/kg (12 ml/kg) Gd-DOTA and 200 mg/kg (2.5 ml/kg) Acetazolamide. A 3D inversion recovery (IR) prepared MDEFT sequence (ParaVision 5.0, FOV 15 × 15 mm^2, matrix 32 × 32, 8 coronal slices × 0.7 mm) was used with TE = 1.2 ms, TR_{echo} = 6.5 ms, excitation flip angle = 10° [4] and a non-selective adiabatic inversion pulse. The Gd-DOTA and the vasodilator were injected at 5 minutes and at 35 minutes (during the measurement time window), respectively, after the start of a dynamic $RSST_1$ acquisition (TR = 750 ms, T_{inv} = 303 ms, 6 s per repetition) lasting 65 minutes. The signal was normalized according to $S_{norm}(t) = (S_{post}(t) - \langle S_{pre} \rangle)/S_0$, where $S_{post}(t)$ is the post contrast signal and $\langle S_{pre} \rangle$ is the average pre contrast signal. S_0 is the signal in a proton density weighted image (TR = 10 s, T_{inv} = 9 s, duration 1 min 20 s) acquired prior to Gd-DOTA injection providing the equilibrium signal from the vascular and extravascular compartment. In brain tissue with intact blood brain barrier, the normalized signal $S_{norm}(t)$ equals the BVf since the contrast agent is confined to the intravascular space during the measurement time window [4,6]. Statistical significance ($p < 0.05$) was tested with a one-sample t-test using the average BVf before Acetazolamide injection as hypothetical value.

Results and discussion: The signal steady state starts 15 minutes after intraperitoneal Gd-DOTA injection enabling the measurement of a baseline cerebral BVf before the Acetazolamide is administered 10 minutes later. The chart in Figure 1 shows the average BVf in a region of interest located in the thalamus (6.0 ± 1.5 mm^2), which is 0.02 ± 0.002 at baseline and increases continuously after Acetazolamide administration. The cerebral BVf increase is already significant at 5 minutes post injection. This finding confirms the confinement of the Gd-DOTA to the vascular compartment. In tissues such as muscle, where Gd-DOTA extravasates, the signal is not sensitive to vasodilation. Figure 2a shows a typical cerebral BVf map at bregma -1.6 mm with the thalamus outlined on the right hemisphere. Figure 2b shows a corresponding T_2-weighted image for anatomical reference.

Conclusion: In this study, we show that quantitative cerebral BVf measurement with the $RSST_1$-technique and i.p injection of Gd-DOTA is feasible and has two advantages: it is less traumatic for the mice and increases the time window for BVf measurement. This time window was used to demonstrate the sensitivity of the $RSST_1$-technique by increasing the BVf pharmacologically. This study also confirms the vascular confinement of Gd-DOTA in cerebral tissue after i.p. injection. The $RSST_1$-technique can be used with such a pharmacological MRI protocol to study the vasoreactivity to other drugs in healthy mice or in neurological models with an intact blood brain barrier [3].

Fig. 1:

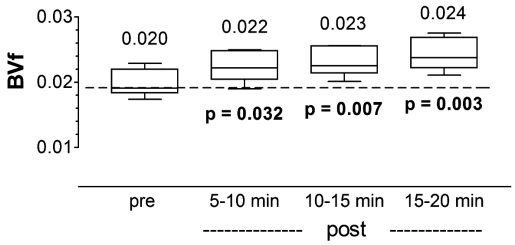
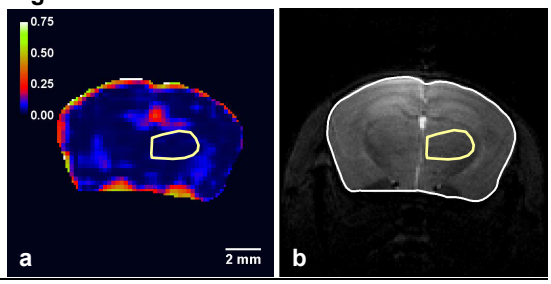


Fig. 2:



[1] Aronen et al, Radiology 1994; [2] Perles-Barbacaru et al, NMR Biomed 2011; [3] Perles-Barbacaru et al, Neuroimage 2011; [4] Perles-Barbacaru and Lahrech, J Cereb Blood Flow Metab 2007; [5] Moreno et al, NMR Biomed 2006; [6] Perles-Barbacaru et al, ISMRM 2011, #2143