Validation of cerebral blood volume quantification in humans by Rapid Steady State T_1 MRI

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TARGET AUDIENCE: basic scientists and clinicians

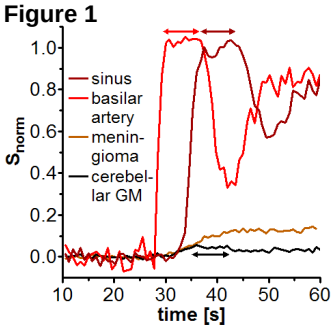
PURPOSE: Noninvasive quantification of the blood volume fraction (BVf), an imaging biomarker of angiogenesis, is of great importance for tumor grading and treatment monitoring, particularly when using antiangiogenic agents. Existing MRI methods either monitor the first pass of a contrast agent (CA) bolus in the tissue of interest or acquire the signal when the vascular CA concentration is in a steady state (SS). Quantification of the BVf with dynamic susceptibility or contrast enhanced techniques is complicated by the need of a simultaneous measurement of the blood CA concentration, the arterial input function (AIF). Consequently, in clinical routine, BVf measurements are often relative, precluding inter-patient and intra-patient comparisons in clinical and serial studies, respectively. Tumor BVf quantification with slower SS techniques is particularly affected by the transendothelial leakage of low molecular size CA such as Gd-DOTA. The Rapid Steady State T_1 ($RSST_1$) MRI technique[1] circumvents some of these disadvantages, by exploiting a vascular signal that is independent of the AIF. Using the $RSST_1$ technique quantitative BVf maps of healthy rat, mouse and monkey brains have been acquired with experimental high relaxivity CA and with Gd-DOTA.[1,2] Tumor BVf quantifications with an experimental blood pool CA (gadolinium-chelating cyclodextrin) and iron oxide nanoparticles have been validated with independent techniques.[3] The $RSST_1$ technique being a dynamic technique with high temporal resolution (< 1 second), the signal increase during CA accumulation in the extravascular compartment can be modeled to derive the tumor BVf.[4]

Here, we present the clinical transfer of the $RSST_1$ method using the clinically approved CA Gd-DOTA.

METHODS: With approval by the Research Ethics Committee, the $RSST_1$ technique is included in the neuroimaging examination of neurooncological patients (n=15) requiring Gd-DOTA administration for routine follow up. Gd-DOTA is administered at a dose of 0.1 - 0.2 mmol/kg using an automatic injector (3 mmol/s) during a dynamic (NR=120, duration 90s) single-shot 2D turbo-field-echo acquisition (non-selective inversion pulse, $T_{inv}/TR/TR_{echo}/TE/\alpha$ = 325ms/750ms/4ms/1.27ms/10deg, 64×55 matrix) on a Philips Achieva scanner at 1.5T. The signal is normalized according to $S_{norm}(t)=(S_{post}(t)-\langle S_{pre}\rangle)/S_0$, where $S_{post}(t)$ is the post-contrast signal, $\langle S_{pre}\rangle$ is the average pre-contrast signal, and S_0 is the equilibrium signal from the vascular and extravascular compartment acquired in 30s with TR/NR=10s/3 using the same sequence without inversion pulse.

RESULTS: Appropriate acquisition parameters make the MRI sequence act like a low pass filter for the longitudinal relaxation time T_1, resulting in selective acquisition of tissue compartments in contact with the T_1-shortening CA.[1] At 1.5T, S_{pre} is ≈0 for tissues with $T_1 \geq$ 900ms such as blood ($T_1 \approx$ 1250ms)[5] and cortical gray matter. For a dose ≥ 0.13 mmol/kg (n=13), which is acceptable in clinics, $S_{norm}(t)$ in blood and brain tissue with Gd-DOTA confined to the vascular space reaches a SS at maximum amplitude lasting ≈ 8s during which BVf = S_{norm} (arrows in Figure 1). In large vessels without partial volume effect (venous sinus and basilar artery) a BVf ≈1 was obtained validating the measure for vasculature on a subvoxel scale such as in cerebral tissue. BVf in the range of 0.035 to 0.045 and 0.015 to 0.02 were measured in healthy appearing gray matter and white matter, respectively. With the spatial resolution of 3.5mm×3.5mm×6mm and due to the partial volume effect, the S_{norm} SS amplitude was always ≤ 0.6 in a voxel containing the anterior or middle cerebral artery. A S_{norm} SS was also observed for low grade tumors and some parts of high grade tumors. For these tissues, assuming insignificant CA leakage during the first pass one can approximate BVf ≈ S_{norm}. The presence of Gd-DOTA permeable vasculature can be easily detected as a continuously increasing S_{norm} signal during the vascular SS as shown for meningioma tissue in Figure 1.

Figure 1



DISCUSSION: In healthy brain tissue, the vascular confinement of the CAs leads to a SS signal during the first pass allowing direct quantification of the cerebral BVf. Since acquisition of the AIF is not required the signal from cerebral vessels can be used to determine the SS duration despite partial volume effects. For direct BVf quantification in tumor tissue appropriate blood pool CA for clinical use are under development. Alternatively, the $RSST_1$ technique can monitor CA accumulation in tumor tissue dynamically in order to apply corrections or approximate the tumor BVf as the S_{norm} amplitude in the beginning of the SS signal in tissue.[4]

CONCLUSION: The $RSST_1$ technique for BVf mapping is powerful for serial clinical studies, because it is quantitative, straightforward, easily transferable to clinical scanners, and because it can be applied with clinically approved CAs.

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