Rapid steady state T1 method for cerebral blood volume fraction mapping: sensitivity determination under hypercapnia

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Introduction

A rapid steady state T_1 method for mapping the cerebral blood volume fraction (CBV) has been described (1). Here, after quantification of the influence of extra-/intravascular water exchange and of transverse relaxation effects, the sensitivity of this method is illustrated by means of hypercapnia experiments in the rat brain.
For this study, P760 (experimental Gd-contrast agent (CA) from Guerbet Laboratories) was used for its high r_1-relaxivity, and Gd-DOTA for being a CA approved for human studies.

Methods

The rapid steady state T_1 method is based on a two-compartment model of the brain (extra- and intravascular) and on the effects of paramagnetic, vascular CA on the longitudinal relaxation T_1 of the blood. A 2D Inversion-Recovery-FLASH sequence is used with a repetition time of 750 ms and an inversion time T_{inv} = 325 ms. With these parameters the extravascular signal (T_1 greater than about 1 s) is suppressed. In the presence of an adequate dose of CA, the blood signal ($T_1 \leq T_{inv}/5$) relaxes back to its equilibrium value within T_{inv}. In these experiments, 0.1 mmol/kg of P760 (or 0.2-0.3 mmol/kg of Gd-DOTA) are intravenously injected. As long as the T_1 of blood is $< T_{inv}/5$, the blood signal remains independent of its T_1 value. Therefore, for 1-5 minutes depending on the CA dose, repeated acquisitions measure a steady signal corresponding to the equilibrium magnetization of the blood, in the absence of any R_2-attenuation and water exchange effects. The echo time (TE) was 3.2 ms. One central coronal slice including structures of the midbrain and parietal and temporal cortex has been acquired for each rat (image resolution $2 \times 0.75 \times 0.75$ mm^3). The experiments were performed in a 2.35 T superconducting horizontal bore magnet of 40 cm diameter (Bruker) using a homogeneous radiofrequency coil for excitation and a surface coil for detection.
The impact of water exchange across the blood brain barrier was evaluated according to the model described by Moran and Prato (2). In order to assess the transversal relaxation effect, *in vitro* measurements on tubes filled with blood sampled before and after P760 injection were carried out and compared to the signal modelization.
For CBV measurements under hypercapnia, eight healthy male Sprague Dawley rats (320 to 450 g) anesthetized with 1.3 to 1.8% isoflurane were mechanically ventilated at a frequency of 60 /min. Pulmonary and arterial blood pressures were monitored throughout the experiment. Arterial hemoglobin, pH and blood gas levels were measured and corrected for rectal temperature before and after each CA injection with the use of a pH/blood gas analyzer (Radiometer Copenhagen ABL™ 510). A first CBV measure was performed under air/oxygen 65%/35% mixture. Graded hypercapnia was induced with addition of 5 to 7% CO_2 during 30 to 45 minutes, while the oxygen flow was maintained, leading to partial arterial carbon dioxide tensions (P_aCO_2) up to 104 mmHg. Up to three CBV measures were performed under different levels of hypercapnia every 15 minutes, following injections of the same amount of CA. 40 minutes recovery from hypercapnia under air/oxygen 65%/35% ventilation was allowed before a final measurement. Assuming a linear relationship between the global CBV (region of interest covering the whole brain slice) and the P_aCO_2, the results of the hypercapnia experiments are represented as CBV changes relative to the individual normocapnic (P_aCO_2 = 40 mmHg) CBV (3).

Results

Fig. 1 is a representative CBV map of the imaged slice obtained with P760 under normocapnic conditions. Mean global CBV was 3.22 ± 0.41% when measured with P760 (n = 7 rats) and 3.37 ± 0.41% when measured with Gd-DOTA (n = 4) (1). These results are not corrected for transverse relaxation and extravscular/intravascular exchange.
The modelization of the signal and the *in vitro* measurements show that the transversal relaxivity effects account for an underestimation of the CBV which is in the order of 15 % with P760 in the blood samples, but are negligible in the microvasculature. The water exchange across the blood brain barrier leads to an overestimation of about 10%.
Fig. 2 shows the global CBV response to hypercapnia. The CBV reactivity measured with P760 and Gd-DOTA bolus injections is identical and about 1% per mmHg P_aCO_2. Regional analysis reveals that the reactivity to hypercapnia is strongest in the cortex (1.3% per mmHg, n = 8 Gd-DOTA and P760 experiments combined). The CBV change is completely reversible after recovery from hypercapnia.

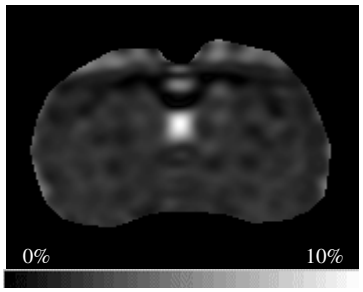

Fig. 1: CBV map of a rat. Global CBV = 3.30 % including the central vein

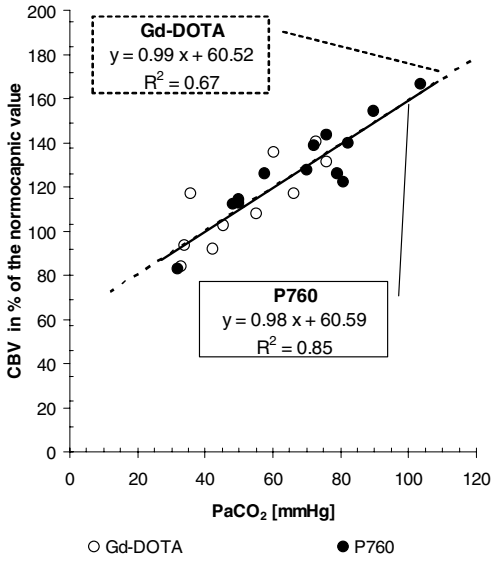

Fig. 2: CBV as a function of the P_aCO_2

Discussion/Conclusion

The rapid steady state T_1 method is simple, direct, insensitive to inflow-outflow effects and does not require determination of the arterial input function.
The normocapnic CBV values obtained are in good agreement with published values. When expressing absolute CBV values, T_2 attenuation and water exchange across the blood brain barrier have to be taken into account, but do not exceed 15% with P760.
The hypercapnia measurements demonstrate the sensitivity of the method to physiologic CBV variations, although isoflurane anesthesia may have attenuated the cerebrovascular response to hypercapnia as it acts like a vasodilator itself. The CBV changes with P_aCO_2 are equally in accordance with the literature. The results ensure that the method will allow monitoring the much greater CBV variations occurring during tumor growth or with other cerebral pathologies.
It has been shown that the method performs equally well with Gd-DOTA at doses well tolerated by human. Thus, the method is applicable to human studies, in which case a good spatial resolution can be achieved, and regional CBV measures would be less affected by the partial volume effect.

References

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