Permeability of the Blood-Brain Barrier to Mn^{++} and Gd-DOTA in a Rat Model of Reversible Ischemia

E. L. Barbier[1], E. Grillon[1], C. Segebarth[1], C. Rémy[1]
[1]UM594, Inserm / Université Joseph Fourier, Grenoble, France

Introduction

MRI studies show that the blood-brain barrier (BBB) becomes permeable to Gd-DTPA after one or two hours of middle cerebral artery (MCA) occlusion (1). However, The BBB might have a differential permeability with regard to the type of contrast agent, in particular its size or charge. In the present study, the extravasation of two contrast agents of different sizes, Mn^{++} (55g/mol) and Gd-DOTA (590g/mol), are compared in a rat model of reversible occlusion of the MCA.

Material and Methods

A total of 26 adult male Sprague-Dawley rats (317±16g) was used in this study. They were divided into three groups, based on the MCA occlusion duration: 30min (n=8), 1h30min (n=8), and 2h30 (n=10). Focal brain ischemia was induced by occlusion of the right MCA using the intraluminal suture model (2). Rats were artificially ventilated. Anesthesia was maintained with an intraperitoneal infusion of chloral hydrate. Rectal temperature was maintained at 37°C. At reperfusion time, the filament was pulled without moving the animal.

After installing the animal in a 7T magnet, an angiogram was acquired to assess MCA occlusion, except for the 30min occlusion group. After verifying the MCA reperfusion with a second angiogram, T_1 maps were produced every 53s during 40min using an inversion recovery FLASH sequence (8 inversion times, TR=5s, field of view= 40mm, matrix= 64^2, slice thickness=2mm). For 16 animals (n=4 in the 30min group, n=5 in the 1h30min group, and n=7 in the 2h30min group) an intravenous infusion of Mn^{++} (100 mM, 1.2ml/h) was started after 6min of T_1 acquisition; 15min later, a T_1-weighted spin-echo dataset was acquired. Then, T_1 monitoring was resumed and after 1min, an intra-arterial bolus of Gd-DOTA was injected (0.2mmol/kg) and flushed with saline. As the venous catheter was filled with Mn^{++}, the arterial way was chosen to inject the Gd-DOTA in order to avoid a sudden afflux of Mn^{++} into the heart (susceptible to provoke a cardiac arrest). For the remaining 10 animals, no contrast agent was injected.

Results

For all animals, systemic physiological parameters were within normal limits. Fig. 1 shows the T_1 evolution for the three occlusion durations in both the ipsilateral and contralateral hemispheres and for the animals which received contrast agents (top row) and for the controls (bottom row). Fig. 2 shows the T_1 values measured at different time points for the animals that received contrast agents (top row) or not (bottom row). It can be seen that both contrast agents yield a T_1 reduction in both contralateral and ipsilateral regions. However, in the ipsilateral region, the T_1 reduction is larger (for both Mn^{++} and Gd) than contralaterally. The T_1 reduction for the 30min occlusion group is smaller than for the two other occlusion durations. For the animal without contrast agents, it can be observed that T_1 increases after reperfusion for the 1h30min and 2h30min occlusion groups but not for the 30min occlusion group.

Conclusions

It appears that even for a short occlusion duration, contrast agents may leak through the BBB. For longer occlusion durations, the T_1 reduction due to the contrast agent becomes larger. The T_1 reduction observed in the 30min occlusion group may however be too small to be detected by classical T_1-weighted sequences. The data processing performed so far does not allow differentiating the behavior of Mn^{++} and Gd-DTPA in the ischemic lesion. Using a model, it should be possible to extrapolate the behavior of tissue T_1 as the Mn^{++} infusion continues and thereby, access the BBB permeability to both contrast agents.

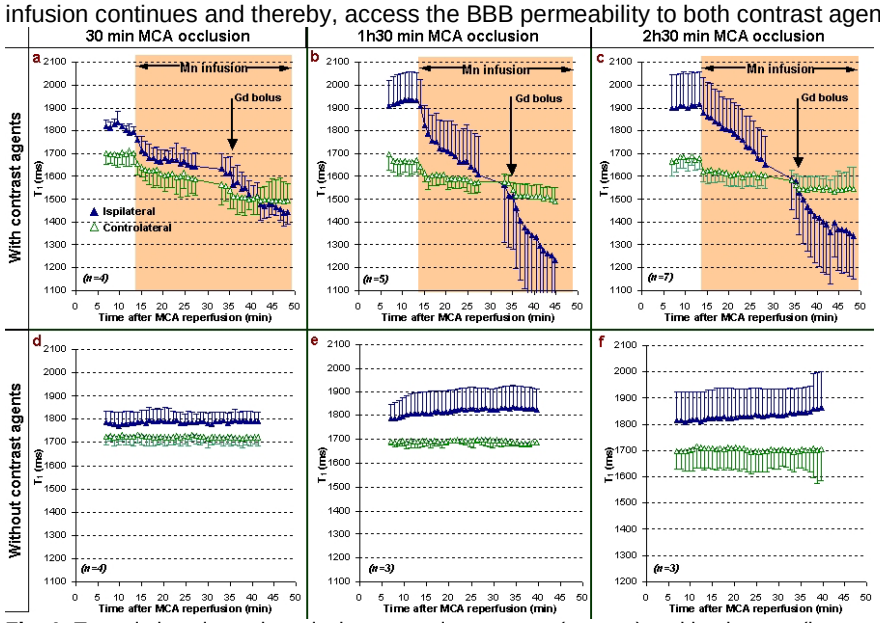

Fig. 1. T_1 evolutions in each occlusion group, in presence (top row) and in absence (bottom row) of contrast agent, and for the ipsilateral (black) and contralateral (white) regions of interest. Graphs **a**, **d**: 30min occlusion; **b**, **e**: 1h30min occlusion; **c**, **f**: 2h30min occlusion.

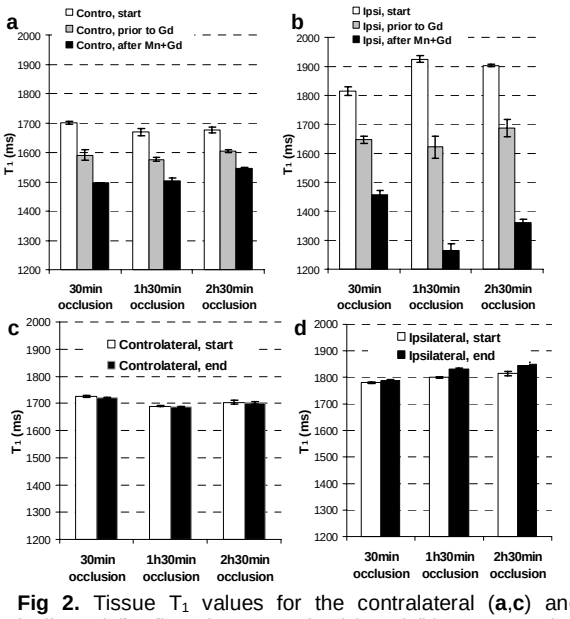

Fig 2. Tissue T_1 values for the contralateral (**a**,**c**) and ipsilateral (**b, d**) regions. Graphs (a) and (b) correspond to the animals that received contrast agents; Graphs (c) and (d) to the animals that did not receive contrast agents.

References

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2. Longa EZ *et al*. Stroke 1989;20:84-91.