AGE-DEPENDENT DECREASE OF CAPILLARY DENSITY IN ARCABETA MOUSE MODEL OF CEREBRAL AMYLOIDOSIS DETECTED WITH RELAXATION RATE SHIFT INDEX Q MAPPING AT 9.4T USING A CRYOPROBE

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Introduction: Alzheimer's Disease is accompanied by morphological and functional changes of the cerebral vasculature[1,2,3].Magnetic Resonance Imaging (MRI) offers widespread and reliable methods to investigate the brain vasculature *in vivo*. The aim of this study is to use relaxation rate shift index Q to investigate the density of cerebral microvasculature and bolus tracking for assessing the perfusion state in the arcAβ mouse model of cerebral amyloidosis.

Materials and Methods: For all measurements a BioSpec 94/30 (Bruker BioSpin MRI GmbH Ettlingen, Germany) operating at 400MHz and equipped with a cryogenic phased-array coil (Bruker BioSpin AG, Faellanden, Switzerland) was used. Twelve-months-old (n=15) and 24-months-old (n=13) arcAβ and wt mice of either sex, were measured[5]. Anesthesia was induced with 3% isoflurane in a 1:4 oxygen:air mixture and maintained at 1.5% isoflurane. Mice were endotracheally intubated and mechanically ventilated. Additionally, mice were cannulated on the tail vein to allow the injection of the contrast agent. Temperature was monitored and kept constant at 36±0.5°C. Mice were injected with Endorem (Guerbet) at the dose of 30 mgFe/kg. After the acquisition of anatomical scans 3 axial slices 0.6 mm thick with a 0.6 mm gap were positioned on the brain and a 2D SE TurboRARE with the following parameters was acquired: T_E/T_R = 30/2000ms, α = 90°, bandwidth = 50kHz, NA = 6, matrix size 192 x 192 with a field of view of 1.92 x 1.92 cm to give a 100μm^2 resolution.Acquisition time was 5min. A 3D gradient echo (GE) FLASH sequence was used with the following parameters: T_E/T_R = 5.5/40 ms, α = 5°, bandwidth = 50kHz, NA = 8, matrix size 192 x 192 x 40 with a field of view of 1.92 x 1.92 cm to give a 100μm^3 resolution, 4 mm slab coronal.The acquisition time was 40 min. The geometry was arranged to have the same isodistance and offcenter for both sequences. The two sequences were recorded pre- and post-contrast agent injection. For bolus tracking, an echo planar imaging (EPI) sequence with 12 coronal slices was acquired using the following parameters: T_E/T_R = 9.960/400 ms, bandwidth = 238095Hz, NA = 1, with 300 repetitions matrix size 64 x 64, FOV = 2.37 x 1.4 cm, acquisition time was 2 min. The bolus was injected 30 s after scan start. For the computation of the Q maps the transverse relaxation rates were calculated for the spin and GE images, computing the ΔR_2 as $1/T_E \times \ln(S_{pre}/S_{post})$ and the ΔR^*_2 as $1/T_E \times \ln(S^*_{pre}/S^*_{post})$, the index Q is than calculated as following $Q = \Delta R_2/(\Delta R^*_2)^{2/3}$. From the dynamic EPI sequence, cerebral blood flow (CBF) and cerebral blood volume (CBV) were extracted.

Results: Typical Q maps of a wt mouse are depicted in Figure 1. Variance of Q values in the brain of wt mice was 20%, similar to what has been reported recently[4] , For 24-months-old mice a statistically significant reduced Q index was found in the cortex and cerebellum of arcAβ mice compared to wt mice (p = 0.001 and p = 0.0152, respectively) (Fig.2a). In 12 months-old-mice we found a statistically significant difference only in the hippocampus, where arcAβ mice showed higher Q values compared to wt mice (0.687 ± 0.258 vs. 0.516 ± 0.128, p=0.016) (Fig.2b). CBF values were found to be lower in the cerebellum of 24-months-old arcAβ mice compared to wt mice (0.451 ± 0.166 vs 0.705 ± 0.177, p=0.016) (Fig.3a), while they were not statistically different in the other brain regions. In contrast, CBV values were found to be higher in the cortex of 24 months-old mice arcAβ compared to wt controls (0.431±0.1 vs. 0.354 ± 0.049, p=0.016) (Fig.3b).

Conclusions: relaxation rate shift index Q constitutes a powerful method to non-invasively estimate brain capillary density. We found an age-dependent decrease of the Q values in arcAβ mice, indicative of a loss of functional microvessels due to Aβ pathology. This is in accordance with the literature where it has been shown that the amyloid pathology affects more the microvessels than large blood vessels[1,3] Qmaps might provide a better indicator of capillary vasculopathy compared to perfusion MRI, as the latter is more sensitive to contributions from large vessels. An histological validation study is being currently conducted to investigate the cause of capillary density reduction in arcAβ mice.

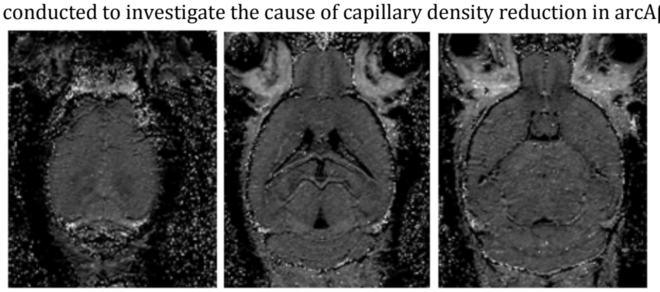

Figure 1 Q-maps of an ArcAbeta mouse brain. Three horizontal sections of a slice thickness of 0.6mm are shown comprising brain structures such as the cortex, olfactory bulb, hippocampus, striatum, thalamus and cerebellum.

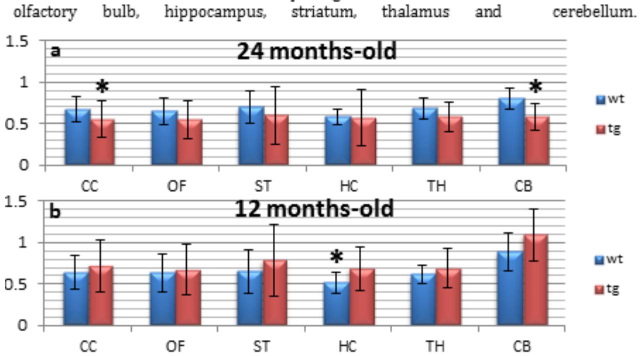

Figure 2 Quantitative analysis of Q-maps for selected regions-of-interest for wt (blue) and ArcAbeta mice (red). Statistically significant differences are indicated by an asterisk (p<0.05). CC=cortex ,OF=olfactory bulb, ST=striatum ,HC=hippocampus, TH=thalamus, CB=cerebellum. Data shown as mean ±SD

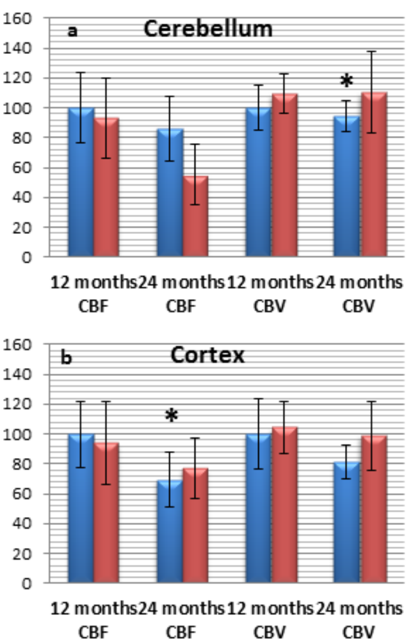

Figure 3 Relative CBF and CBV values for cortical and cerebellar region-of-interest for wt (blue) and transgenic mice (red). Data were normalized on 12-months-old wt mice values

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