Comparison of baseline cerebrovascular changes between eNOS knockout and wild type mice

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Introduction: Endothelia-derived nitric oxide (NO) is important for properly regulating vascular tone and maintaining blood pressure. Mice lacking endothelia NO synthase (eNOS), i.e. loss of endothelial NO production, have systemic hypertension and tend to develop relatively large cerebral infarction upon cerebral ischemia.(1) Despite the extensive studies performed using eNOS knockout (KO) mouse models and numerous evidences indicating vascular abnormalities, baseline cerebrovascular parameters of the eNOS KO mice have not been fully documented. In this study, we aim to establish MRI-derived vascular parameters (cerebral blood volume, transvascular water exchange, and cerebral vessel size) in eNOS KO mice using two different MRI intravascular contrast agents (Gd-PGC and superparamagnetic iron oxide nanoparticle (SPION)) and to compare these basal vascular parameters with those in wild type (WT) mice.

Materials and Method: Eight C57BL/6 and five eNOS KO mice were used in this study. A 3D SPGR (spoiled gradient echo) pulse sequence was used for quantifying absolute cerebral blood volume (CBV) and transvascular water exchange using a 9.4T scanner (Bruker Biospin). Before and after intravenous administration of Gd-PGC, 3D volume images (Matrix: 64 x 64 x 128, FOV: 1.5 x 1.5 x 2.5 cm) were collected with TR/TE = 30/3 ms with varying flip angle = 30 and 90° degrees. Additional 3D-SPGR scans with TR/TE = 30/5, 7 ms at a fixed flip angle of 30° were also performed to calculate changes in T_2* due to Gd-PGC. After CBV and water exchange measurements, SPION was intravenously administered for average cerebral vessel size measurement. ROI analysis was performed in the cerebral cortex. The apparent blood volume was calculated based on: $V_{app}^{\alpha} = \frac{SI_{postGd-PGC}^{tisue} - SI_{preGd-PGC}^{tisue}}{SI_{postGd-PGC}^{blood} - SI_{preGd-PGC}^{blood}}$, where *SI* is the signal intensity and α is the flip angle. Water exchange index (WEI) is defined as the following: $WEI = V_{app}^{30} / V_{app}^{90}$.(2,3) While, the absolute CBV was estimated using V measured using α = 90°. Vessel size index (VSI) was calculated using the following relationship: $VSI = \Delta R_2^* / \Delta R_2$ (4).

Results and Discussion: In general, there is no apparent anatomical difference between eNOS KO and WT mice as shown in T_2-weighted images (Figure 1). eNOS KO mice have a smaller average vessel size at the cortical level than that in WT mice (Figure 2A). Contrary to what we expected from the apparent reduction in vascular caliber, the CBV of eNOS KO mice was not significantly different from that of WT mice, suggesting an increase of average cerebral vessel density in the eNOS KO mice (Figure 2B). Furthermore, baseline WEI significantly increased in the eNOS KO mice, indicating higher BBB water permeability. These results suggest that the loss of eNOS does not only contribute to the alteration of vascular geometry (i.e., vessel radius) but also affects vascular function (i.e., increase water permeability) even under a normal physiological condition. Understanding such abnormalities in baseline cerebrovascular parameters in eNOS KO mouse models will further aid the investigation of eNOS functions under pathological conditions including hypertension.

References: 1. Huang, PL, Science, 1995, 2. Kim, YR, MRM 2002. 3. Kim, YR, MRM 2008, 4. Boxerman, J. MRM 1995

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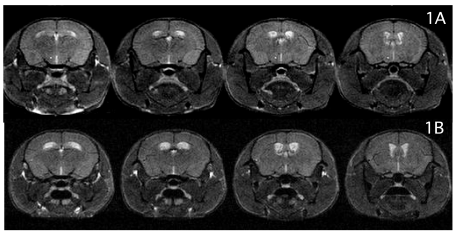

Figure 1: T_2-weighted images of wild type (1A) and eNOS KO mouse (1B)

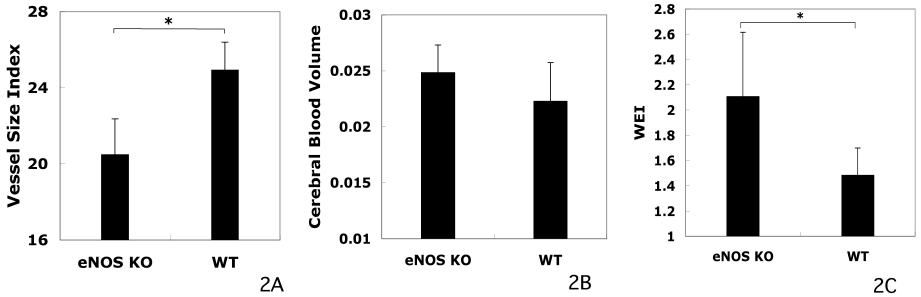

Figure 2: comparison of Vessel size index (2A), CBV (2B), and WEI (2C) of eNOS KO and WT mice.