Cerebral Blood Flow and Vascular Reactivity in Progressive Hypertension

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Target Audience: neuroscientists and hypertension researchers

PURPOSE: Chronic hypertension increases susceptibility to neurological disorders. The goal of this study was to evaluate cerebral blood flow (CBF) and cerebrovascular reactivity (CR) in response to hypercapnia in an established rat model of hypertension (SHR) at different stages of the disease progression. Comparisons were made with age-matched normotensive Wistar Kyoto (WKY) rats.

METHODS: Male SHR and WKY rats (Charles River) were studied with IACUC approval in six groups: i) 10-week (N=6, 8~10 weeks), ii) 20-week (N=6, 18~20 weeks), iii) 40-week (N=8, 38~40 weeks) old SHR rats, and the corresponding three age-matched WKY control groups with N=6 each. Body weight, heart rate and tail mean-arterial-blood pressure (MABP) in awake conditions were measured before each MRI section. Hypercapnic challenge for CR study used 5% CO2.

MRI was performed on an 11.7-Tesla Bruker Biospec scanner with a surface coil for brain imaging and a neck coil for arterial-spin labeling. T_2-weighted MRI employed a fast spin-echo sequence with 3s 8 TR, 90ms effective TE, 4 echo-train length, 25.6x25.6mm^2 FOV, 96x96 matrix, 8 1.5-mm slices, and 8 averages. CBF employed continuous ASL with four-shot, gradient-echo planar imaging with 25.6x25.6cm^2 FOV, 96x96 matrix, 8 1.5-mm slices, TE=12ms, TR=3s per shot, and 60 repetitions.

RESULTS and DISCUSSION: WKY body weight increased significantly with age, heart rate did not change with age, and MABP trended positively with age. Body weight was not statistically different between SHR and WKY at all stages. Differences in heart rate and MABP between SHR and age-matched WKY were present at 10 weeks, and grew progressively larger with age.

T_2-weighted images with three overlaid ROIs of the basilar artery (BA), middle cerebral artery (MCA) and anterior communicating artery (ACA) territories used for quantitative analysis are shown in **Fig 1A**. CBF images showed heterogeneous contrasts (**Fig 1B**, scale bar: 0-2 ml/g/min). Hypercapnia-induced CBF changes are shown for 40-week animals in **Fig 1C**. In 40-week WKY, CBF %-change maps showed positive responses. In contrast, some 40-week SHR showed expected hypercapnia-induced CBF increase (albeit attenuated compared to WKY) and other 40-week SHR showed unexpected hypercapnia-induced CBF decrease at late stage in the BA territory and part of the MCA territory. The corresponding MRA showed marked stenosis in the BA (blue arrow) and partial stenosis in the MCA (yellow arrow) as well as some stenosis in the ACA (red arrow) (**Fig 1D,** 1: BA, 2: internal carotid artery (ICA), 3: MCA, 4: ACA, 5: posterior cerebral artery (PCA), 6: azygos artery, 7: branch of MCA; 8: branch of PCA**)**. Enlarged pial arterioles of ACA, MCA and PCA (brown arrows) were also observed.

The group-averaged basal CBF values in the whole brain, MCA, ACA and BA territories are shown in **Fig 2A**. WKY CBF generally did not change significantly with age in the territories perfused by the MCA, ACA and BA. By contrast, SHR CBF started out higher than WKY CBF in early stage. In middle stage, the patterns started to reverse and, by late stage, SHR CBF was significantly lower than WKY CBF.

CVR analysis (**Fig 2B**) showed that WKY CVR increased slightly with age in all territories perfused by the MCA, ACA and BA. By contrast, SHR CVR started out higher than WKY CVR and grew progressively larger with age. The differences between WKY and SHR CVR were present at early hypertension and grew markedly larger with age.

Fig 2C shows CBF responses to hypercapnia (symbols indicate P<0.05). WKY CBF responses did not change significantly in the whole brain and the MCA territory with age, but decreased slightly in the ACA and BA territory. By contrast, CBF responses of SHR started out higher than WKY and decreased progressively with age, ending lower than WKY.

CONCLUSIONS Multi-parametric MRI provides non-invasive, clinically relevant data on the cerebral circulation that include hemodynamics and cerebrovascular reactivity. These parameters are altered in early stage of chronic hypertension and worsen with disease progression, ultimately resulting in hypoperfusion and compromised cerebrovascular reserve. MRI has the potential to be used to identify brain regions susceptible to cerebrovascular compromise, improve understanding of disease pathogenesis as well as guide and monitor treatments in hypertension.