4D Flow MRI to quantify cerebral blood flow during environmental challenges

J. Mikhail Kellawan[1], John W Harrell[1], Alejandro Roldan-Alzate[2], Cameron Rousseau[1], Oliver Wieben[2], and William G Schrage[1]

[1]Department of Kinesiology, University of Wisconsin - Madison, Madison, Wisconsin, United States, [2]Departments of Medical Physics and Radiology, University of Wisconsin - Madison, Madison, Wisconsin, United States

Target audience: Clinicians and scientists interested in cerebral hemodynamics, responses to environmental stress (eg. Hypoxia), and the vascular mechanisms responsible.

Introduction: Important clinical conditions such as syncope, hypertension, stroke, vascular dementia, mild cognitive impairment, Alzheimer's disease and other neurodegenerative diseases all have strong cerebral vascular components. While there are well-designed human studies investigating cerebral hemodynamics and assessing control of cerebral vasculature, many of these scientific studies are limited by use of transcranial ultrasound of 1-2 vessels, and only assess velocity changes rather than quantification of flow. Additionally, there is recent evidence that extra-cranial and intra-cranial vessels may respond differently to environmental stressors [1]. Taken together, these highlight a substantial need for technology that allows for simultaneous measurements of multiple vessels and offers quantification of flow within cerebral circulation. Phase contrast 4D-flow MRI methods hold great promise to overcome the challenges associated with comprehensive non-invasive flow measurements in the brain. ***The purpose of this study*** was to quantify changes in total and regional CBF in healthy controls during a hypoxia challenge, as well as test the vascular cyclooxygenase signaling as a potential CBF control mechanism on regionally specific as well as total CBF. ***We hypothesized*** CBF would increase more in anterior compared to posterior circulation. Further, base on animal data we hypothesized the contribution of cyclooxygenase would differ across the cerebral circulation (greatest in middle cerebral artery, MCA).

Methods: In this Ethics Board-approved study, 6 healthy adults (3 males, 3 females, 28 ± 2 years, 77 ± 5kg) were imaged after written informed consent. Scanning was performed after a 10-12 hour fast. Subjects were instrumented to monitor systemic hemodynamics and respiratory gasses; automated sphygmomanometer (blood pressure), arterial pulse oximetry (oxygen saturation), and capnograph for end-tidal CO_2. Subjects visited the MR facility twice, receiving either placebo or oral Indomethacin (100mg) to inhibit cyclooxygenase (COX) in a randomized double blind design. Subjects were fitted with a nose-clip, and a mouthpiece to manipulate air breathing. After baseline 4D MR scans, subjects breathed a 10% oxygen gas mixture to lower arterial oxygen saturation to ~83% while end-tidal CO_2 was maintained at normoxic levels (~37 mm Hg). Steady state hypoxia was achieved within 5 min and maintained for at least 5 more min to repeat 4D measures. ***MR-Imaging.*** Studies were conducted on a clinical 3T scanner (Discovery MR 750, GE Healthcare, Waukesha, WI) with a 32-chanel head coil (NeoCoil, Pewaukee, WI). 4D velocity mapping was achieved using a radially undersampled phase contrast acquisition (5-point PC-VIPR) with increased velocity sensitivity performance and comprehensive coverage of the head [2]. Radial 4D flow MRI image parameters included: imaging volume: 32 x 32 x 24 cm^3, 1.25mm acquired isotropic spatial resolution, TR/TE=6.4/2.2 ms, retrospective ECG gating. No contrast was given. ***4D flow MRI Data Analysis:*** Vessel segmentation was performed in MIMICs (Materialize, Leuven, Belgium) from PC angiograms Flow visualization and measurement including interactive cut-plane measurements were conducted in EnSight (CEI, Apex, NC) **Statistics:** Flow data were acquired at five major arteries: Middle [MCA] x2, Anterior [ACA] x2, and Basilar [BA]. Flow values measured in each vessel were compared before and after the hypoxic challenge using paired Student t-tests. A p-value of 0.05 indicated statistical significance.

Results and Discussion: means ± SD. Segmentation quality of the angiograms demonstrated excellent vascular detail in all cases (Fig.1). Basal CBF was 783 ± 177 ml/min, which increased to 915 ± 237 ml/min, an increase of 131 mL/min (p = 0.01). Statistically significant increases in blood flow were seen in the ACA, MCA and BA (p < 0.02). The largest relative increase in CBF occurred in MCA (Δ 65 ± 32 ml/min). COX inhibition with Indomethacin reduced baseline CBF (456 ± 91 mL/min). The increase in CBF to hypoxia challenge was reduced to 101 mL/min by Indomethacin. Interestingly, the change in CBF with Indomethacin was not uniform. Specifically, Indomethacin did not alter Δ BA flow (Δ BA flow = 25 vs. 28 ml/min, placebo vs. Indomethacin p = 0.8), however, Indomethacin decreased Δ CBF in ACA and MCA (by 10 and 23 ml/min respectively, p < 0.05). These data also suggest the role of COX mediating hypoxic responses is highly sex- and vessel-specific (Fig. 2B).

Summary: High-resolution 4D flow MRI can characterize and quantify blood flow in the entire cerebrovascular system with comprehensive coverage and simultaneous acquisition of a high quality angiogram without need for a contrast agent. This approach uncovered novel sex-by-artery specific CBF responses to hypoxia, a particularly striking finding in the context of sex-specific pathogenesis of many cerebrovascular diseases. Therefore, 4D PC-VIPR has important implications for experimental studies as well as monitoring treatment of patients with various clinical conditions that are associated with poor CBF and high cerebrovascular disease risk.

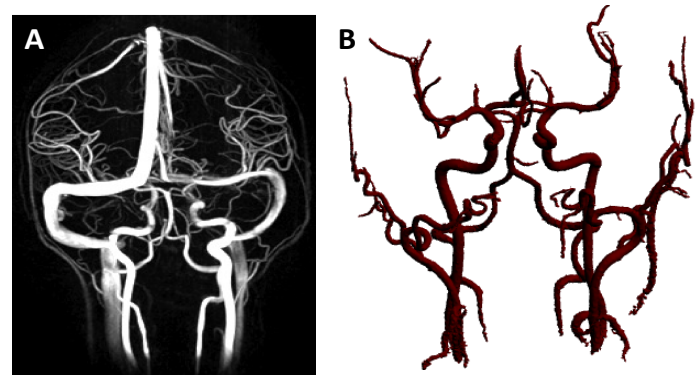**References:** [1] Willie JPHYS 2012 [2] TL Gu et al., AJNR 2005

Figure 1. PC VIPR angiogram displayed as a MIP image showing arteries and veins (a) and as a volume-rendered display after segmentation of the arterial tree (B).
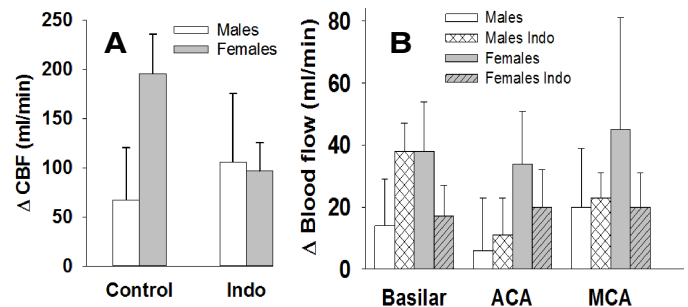

Figure 2. Total and grouped vessel CBF measured by 4D PC VIPR MR sequence.

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