DIFFERENTIAL PATTERNS OF AGE-RELATED CHANGES IN CEREBRAL BLOOD FLOW AND CEREBROVASCULAR REACTIVITY ACROSS THE LIFESPAN

H. Lu[1], Y. Cheng[1], A. Hebrank[2], B. Flicker[2], U. S. Yezhuvath[1], K. Rodrigue[2], K. Kennedy[2], and D. C. Park[2]

[1]Advanced Imaging Research Center, University of Texas Southwestern Medical Center, Dallas, Texas, United States, [2]Center for Brain Health, University of Texas at Dallas, Dallas, Texas, United States

INTRODUCTION: Aging of the brain is often accompanied by changes in cerebral vasculature manifested as arterial stenosis, hypertension, as well as increased risk of stroke. These vascular dysfunctions will affect tissue integrity, neural function, and ultimately cognition. Previous studies have investigated changes in cerebral blood flow (CBF) with aging. However, most of these studies have primarily focused on the comparison between the extreme age groups (e.g. 20s vs. 70s). Middle-aged subjects have typically not been included. More importantly, CBF may not be the right marker for assessment of vascular function, as CBF is often affected by metabolic demand and may not be truly indicative of vessel integrity. Here we hypothesize that cerebrovascular reactivity (CVR) provides a more direct assessment of brain vascular health and displays a different pattern of changes compared to CBF. Two sets of studies were performed: 1) we first performed an initial study to compare CBF between elderly subjects and young subjects and identified brain regions manifesting significant changes; 2) in a second study, we studied subjects with ages across the lifespan, studied their CVR using 5% CO2 breathing, and compared the CVR changes with CBF changes measured in the same group. Decade-by-decade time courses of CBF and CVR changes were also quantified.

METHODS: A total of 53 healthy controls (age 21-79 years) were studied on a 3T scanner (Philips). In the first set of experiments (n=30), whole brain CBF mapping was conducted using a new technique, pseudo-continuous-arterial-spin-labeling (pCASL) (1-3), in a young group (n=22, age 32±11 y) and an elderly group (n=8, age 69±9 y). In the second set of experiments (n=23), a subject group with ages from 21-79 years were studied using 5% CO2 as a vasodilatative challenge for assessment of CVR. This procedure was detailed previously (4). Briefly, the subject breathed room-air and 5% CO2 in an interleaved fashion and BOLD EPI images were acquired continuously at TR of 2s. The end-tidal CO2 trace was recorded throughout the experiments and used as a regressor in the general linear model analysis. The percentage BOLD signal change is normalized against the end-tidal CO2 change, and thus the final CVR is in units of %BOLD/mmHg. In addition, the pCASL CBF measurements were also performed in this group of subjects. Other imaging parameters were: pCASL MRI used TR=4s, labeling duration/delay=1.6/1.5s, voxel size 3x3x5 mm^3, 27 slices, 30 pairs of control/label images, scan duration 4min; CVR scan used TR/TE=2s/30ms, voxel size 3.4x3.4x4 mm^3, scan duration 7 min, air was switched between room-air/CO2 every 1 min (blinded to the subject).

For data processing, CBF was calculated from the pCASL data using a model by Alsop and Detre (5), and was normalized against the whole brain value (thereby reducing inter-subject variations in global CBF). For CVR analysis, SPM was used to perform linear regression, similar to a typical BOLD fMRI study. Both CBF and CVR maps were spatially transformed into the MNI template using HAMMER software (6), which corrects for brain atrophy. Thus, the CBF and CVR maps used for group comparison are partial-volume corrected.

RESULTS and DISCUSSION: Fig. 1a shows the averaged CBF maps in three cross sections. The quality of the CBF maps was satisfactory and covered the whole brain. The CBF deficient regions are primarily located in frontal lobe and anterior cingulate cortex (Fig. 1b). These findings are confirmed by the results from our Study 2 (Fig. 1c). For the CVR scan, 6 subjects declined to participate in the CO2 task. Subjects who participated (n=17) tolerated the CO2 challenge well and many of them did not even feel a change in breathing gas. The averaged CVR map is shown in Fig. 2a. Compared to the CBF results, the CVR deficits (Fig. 2b) involved a much broader areas of the brain, including parietal, temporal and frontal lobes. Interestingly, the occipital lobe appears to be spared from the decline. This pattern is consistent with the findings that occipital lobe shows the least and last brain atrophy and decreased burden of white matter hyperintensities (7). In addition, the fact that CVR deficit pattern is drastically different from the CBF pattern (Figs. 1b and c) suggests that CVR and CBF reflect different aspects of brain physiology.

Fig. 3a shows the decade-by-decade CBF changes. There appears to be an initial decrease of CBF from 20's to 30's, then stability until reaching the 70's. On the other hand, the CVR time course (Fig. 3b) shows that vascular reactivity is relatively intact until reaching about 60's, at which point the CVR shows a gradual decay over the next two decades. This temporal pattern is in excellent agreement with the risk of stroke as a function of age (8).

CVR reflects the ability of blood vessels to dilate upon challenge and is an indicator of vascular reserve. Therefore, CVR is likely a more useful biomarker for vascular function compared to simple baseline blood flow measures. CBF is known to be tightly coupled to metabolism (at least in healthy subjects), thus may be an important marker for neural energy consumption. As such, the differential spatial and temporal patterns of CBF and CVR changes during aging can be explained by their sensitivity to different brain processes (CBF to neural metabolism, CVR to vessel integrity). The combination of these two non-invasive techniques may be a valuable tool in the studies of aging and intervention.

REFERENCES: 1) Garcia ISMRM, 2005; 2) Wu et al. MRM, 58:1020, 2007; 3) Wong MRM, 58:1086, 2007; 4) Yezhuvath et al. ISMRM, 2008; 5) Alsop and Detre, 16: 1236, 1996; 6) Shen and Davatzikos, IEEE Trans. Med. Img, 21:1421, 2002; 7) Raz et al. Neuropsychologv 21:149. 2007: 8) American Heart Association.

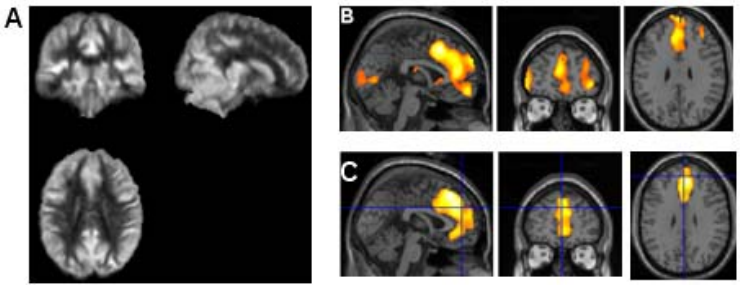

Fig. 1: CBF changes with age. (a) Averaged CBF maps using pCASL MRI. The advantages of pCASL MRI are: completely non-invasive, high sensitivity, covering the whole brain, no special hardware (e.g. tx/rx coil), which is useful in studying elderly population. (b) Regions with CBF reduction from Study 1. Two-sample t test (threshold p<0.005 uncorrected, and cluster size: 150 voxels). (c) Regions with CBF reduction from Study 2. The results from the two separate studies are in excellent agreement.

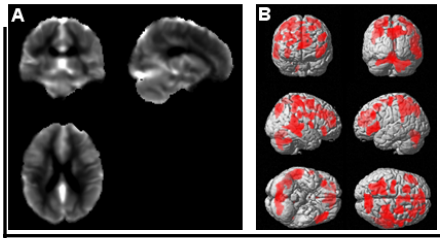

Fig. 2: (a) Averaged CVR map from the CO2 breathing scans. (b) Brain regions showing significant age-dependent decline in cerebrovascular reactivity. The colored regions are rendered on MNI template image using SPM.

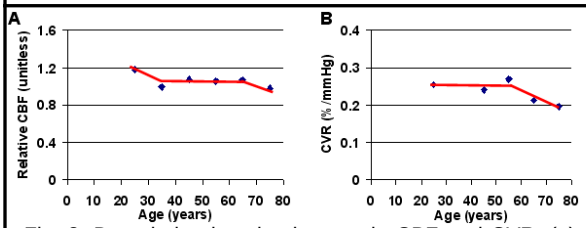

Fig. 3: Decade-by-decade changes in CBF and CVR. (a) CBF change as a function of age (for colored voxels in Fig. 1c). Subjects with age in each decade were grouped to yield one point on the plot. (b) CVR change as a function of age (for colored voxels in Fig. 2b). Because none of the subjects in the CVR study was within the age range of 30-39 years the 30's point is missing in the plot.