Paradoxically reduced cerebral vascular reactivity in Masters Athletes

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INTRODUCTION: Benefits of physical exercise on cardiovascular fitness and cognitive functions are increasingly recognized by researchers and public (1, 2). Efforts are now being directed toward understanding the mechanisms of such salutary effects. Previous research has demonstrated parenchyma changes in the brain including preserved brain mass, structural integrity, and enhanced neural activity during task performance (3, 4). Much of this alteration is thought to be mediated by improvement in cerebrovascular function. However, the effect of physical exercise on vascular health in the brain has not been well characterized and is the topic of this investigation. Furthermore, to probe the upper limit of benefits that one can acquire from exercise, we compared a group of elderly Masters Athletes (MA) to a sedentary elderly group (SED). MA are individuals who participate in competitive sports at a very high level even at an age that exceeds the typical peak age for the event (of course to other athletes in the same age group) and represent a unique group of sample on the highest end of the fitness level spectrum. We used BOLD MRI in combination with CO2 inhalation to measure cerebrovascular reactivity (CVR) in these participants. Baseline cerebral blood flow (CBF) was also determined using Pseudo-Continuous-Arterial-Spin-Labeling (PCASL) MRI.

METHODS: We recruited 10 MA (age = 75 ± 5.8, 7M/3F) from all around the U.S. and 10 SED (age = 75 ± 5.6, 8M/2F). Participants did not have cardiovascular diseases, hypertension, or diabetes, and were not taking any prescription medications. MA had a minimum of 15 years of continuous endurance training; SED were sedentary but otherwise healthy. MRI was performed on a 3T (Philips). CVR was assessed by alternating the breathing of room-air and 5% CO2 (mixed with 21% O_2 and 74%N_2), which is a potent vasodilator. The MR-compatible apparatus was described previously (5). The type of air breathed in was switched every minute in a manner similar to a block design functional MRI experiment, while BOLD MR images were acquired for seven minutes. The BOLD imaging parameters were: TR/TE/FA = 3,000 ms/30 ms/90°, res. = 1.8 x 1.8 x 6 mm^3, FOV= 220 x 220 mm^2, 25 slices. End-tidal CO2 (EtCO2) was measured as an indicator of arterial CO2 level. Data from two MA were discarded due to technical problems. In addition, CBF was measured using the PCASL technique with the following parameters: TR/TE/TI = 3963 ms/14 ms/1500ms, labeling duration 1650ms, res. = 3.0 x 3.0 x 7 mm^3, FOV = 240 x 240 mm^2, 17 slices, duration 4 min.

Data processing: CVR data were processed using a general linear model similar to a typical fMRI scan, except that the regressor was the EtCO2 time-course rather than the fMRI paradigm. $EtCO_2$ time-course provides an input function to the vascular system. The BOLD time-course is the output signal, and by comparing the input and output signals the vascular system property was determined (5). CVR in units of %BOLD signal change per mmHg of Et-CO2 change (%BOLD/mmHg CO2) was determined on a voxel-by-voxel basis. CBF was calculated by subtracting the labeled image from the control image, and the signal was normalized against the whole brain value to obtain a relative CBF map. CVR and CBF maps were spatially transformed to a standard MNI space for comparison across subject groups. Both voxel-based and ROI-based analyses were conducted. Voxel-based comparison used two-sample t test in SPM; a threshold of P<0.01 and minimum cluster size of 200 voxels were used. ROI analysis used pre-defined masks from the AAL atlas which included frontal (Fron), temporal (Temp), parietal (Par), occipital (Occ) lobes, cerebellum (Cereb), insula (Ins), and sub-cortical gray matter (SubC). In calculating the ROI values, two procedures were used to minimize the gray/white matter partial voluming effect. First, Only voxels with a GM probability (using MPRAGE tissue segmentation) of 70% or greater were included in the final mask for averaging. To correct for residual partial volume from the WM, the initial ROI value was further corrected by: $S_{corr} = S_{uncorr}/(GM + (0.4 \times WM))$ (7), where SI_{corr} and SI_{uncorr} are corrected and uncorrected data respectively.

RESULTS and DISCUSSION: $VO2_{Max}$, a measure of maximal uptake of oxygen that represents aerobic fitness level, was 40.6±6.0 ml/kg/min and 23.4±4.1 ml/kg/min for MA and SED subjects, respectively (P<0.0001). Fig. 1a shows group averaged CVR maps. The MA group shows paradoxically lower CVR compared to the SED group. Quantitative analysis using voxel-based comparison revealed that the differences (red voxels in Fig. 1b) are observed throughout the brain. The ROI results are shown in Fig. 1c and demonstrated that a significant reduction is seen in frontal, temporal, parietal lobes, insula and sub-cortical gray matter (P<0.05) with other regions also showing a trend. The largest percentage change was observed in temporal lobe (43%) and the smallest in cerebellum (18%). Neither voxel-based nor ROI based analysis showed any regions where a higher CVR is observed in the MA group. One possible mechanism for the lower CVR in the MA group is that the blood vessels in MA have had more previous exposures to high CO2 levels, as CO2 is a byproduct of metabolism and exercise. Therefore, the vasculature becomes "desensitized" to CO2 stimulation in MA. This hypothesis is in agreement with reports that arterial pressure of CO2 in MA is higher when compared to sedentary elderly subjects (8). For CBF comparisons, it was found that MA had higher CBF in posterior cingulate cortex/precuneus (BA 7) region, a node in the Default-Mode-Network which has been implicated in age-related brain changes and in Alzheimer's disease (9, 10). This finding seems to suggest that long-term physical exercise has a salutary effect in maintaining perfusion and brain activity.

In summary, this work showed a globally reduced CVR to CO2 challenge in MA, compared to SED subjects. However, this difference should not be simply interpreted as a deficit in vascular reserve in MA. Instead, this observation perhaps indicates that MA has a greater potential to tolerate high CO2 level in the blood and brain, and that the reduced vascular response is a protection for the vasculature against over-stimulation due to frequent exposures to CO2. It would be interesting to investigate vascular responses to stimulant other than CO2. For example, a simple visual stimulation could be used and fMRI responses between MA and SED could be compared. Such studies should be conducted in the future.

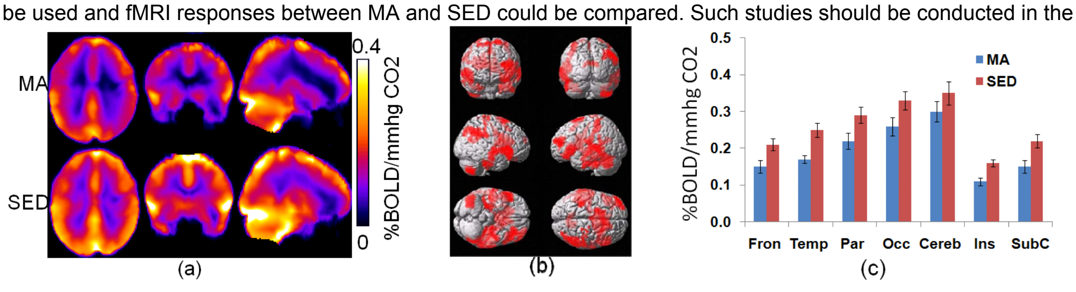

Fig. 1 CVR results: (a) Average CVR maps for MA and SED. (b) Voxel-based comparison between the two groups. Red voxels indicate regions where MA have significantly lower CVR compared to SED (p=0.01, extent threshold of 200 voxels). (c) ROI results: Mean ± SE of CVR values.

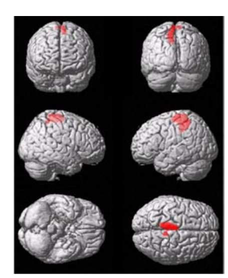

Fig.2 Regions where MA have higher CBF compared to SED (p=0.01, extent 200 voxels).

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