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Cardiorespiratory fitness modifies the relationship between myocardial function and cerebral blood flow in older adults

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ABSTRACT

A growing body of evidence indicates that cardiorespiratory fitness attenuates some age-related cerebral declines. However, little is known about the role that myocardial function plays in this relationship. Brain regions with high resting metabolic rates, such as the default mode network (DMN), may be especially vulnerable to age-related declines in myocardial functions affecting cerebral blood flow (CBF). This study explored the relationship between a measure of myocardial mechanics, global longitudinal strain (GLS), and CBF to the DMN. In addition, we explored how cardiorespiratory affects this relationship. Participants were 30 older adults between the ages of 59 and 69 (mean age = 63.73 years, SD = 2.8). Results indicated that superior cardiorespiratory fitness and myocardial mechanics were positively associated with DMN CBF. Moreover, results of a mediation analysis revealed that the relationship between GLS and DMN CBF was accounted for by individual differences in fitness. Findings suggest that benefits of healthy heart function to brain function are modified by fitness.

Introduction

Growing evidence suggests that physical activity and exercise have protective effects on brain health (Kramer and Erickson, 2007; Smith et al., 2010). Animal models suggest that cardiorespiratory fitness (fitness$_{CR}$) may benefit brain health in part via vascular changes that increase cerebral blood flow, CBF (Swain et al., 2003). However, less is known about the relationship between fitness$_{CR}$ and CBF in humans and how these measures are linked to myocardial function. Global longitudinal strain (GLS), a measure associated with left ventricular myocardial tissue deformation (Hoit, 2011; Reisner et al., 2004), is a strong indicator of myocardial function and is associated with subclinical brain disease in the absence of cardiac disease (Russo et al., 2013). Thus, the predictive power of GLS makes it an ideal proxy of cardiac function when attempting to better understand the relationship between heart health and brain health in older adults.

To date, no study has explored the potential separate and joint contributions of fitness$_{CR}$ and myocardial function to brain CBF. The default mode network (DMN) is a set of intrinsically connected regions that are most active when not specifically engaged in an externally directed cognitive task (Buckner et al., 2008; Buckner and Carroll, 2007; Dixon et al., 2014). The DMN includes the medial prefrontal cortex (mPFC), anterior and posterior cingulate cortex (ACC/PCC), and medial temporal cortex, regions that show disproportionately high resting metabolic rates (Buckner et al., 2008; Gusnard and Raichle, 2001) and susceptibility to healthy aging and Alzheimer's disease (Buckner et al., 2005; Koch et al., 2010). The DMN is therefore an ideal target to determine these relationships using ASL-MRI.

In the present study, we explored the relationship between fitness$_{CR}$ and CBF to the DMN using an independent component analysis (ICA) to identify the DMN in an unbiased manner. In addition, we explored the role of myocardial function in CBF to the DMN. Declines in cardiac function are associated with accelerated brain aging (Jefferson et al., 2010) and precede disease processes characterized by declines in cognitive function, such as Alzheimer's disease (de la Torre, 2009, 2010). However, training-induced increases in fitness$_{CR}$ are associated with augmented

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maximal cardiac output and not resting cardiac output (Ehsani et al., 1991; Stratton et al., 1994), suggesting that improving $fitness_{CR}$ through regular physical activity may help to protect the brain from age-related declines in resting cardiac function.

Methods

Participants

Forty-two community dwelling healthy volunteers (14 males) participated in this study (mean age = 63.89 years, SD = 2.94). Participants provided written informed consent in a manner approved by the University of Kentucky Institutional Review Board and were monetarily rewarded for participating. Twelve of these 42 participants (5 male) were excluded from the study. Of these twelve participants five did not complete the treadmill test because they were either currently taking a beta-blocker, they reported a history of cardiac ablation, or the supervising cardiologist terminated the test due to an abnormal electrocardiogram (ECG). One participant voluntarily terminated the test due to mouthpiece discomfort and another participant was unable to complete the MRI scan due to the presence of a scleral buckle. The remaining 5 participants were excluded because they failed to achieve VO_2 peak (described below).

The 30 remaining participants (9 males) ranged in age from 59 to 69 (mean age = 63.73 years, SD = 2.8). Participants met all criteria for participating in a magnetic resonance imaging (MRI) study. Exclusion for the MRI study included history of a major head injury and/or concussion, neurological disorder (e.g., stroke, seizure), or the presence of metal fragments and/or metallic implants that could cause bodily injury or disrupt the magnetic field. All participants also met all criteria for participating in a maximal graded exercise test. Exclusion for the graded exercise test included a diagnosis of any major medical condition (e.g., heart, lung, or kidney disease), a history of uncontrolled high blood pressure, uncontrolled diabetes, a history of heart complications (e.g., heart murmur or coronary artery disease), pulmonary dysfunction (e.g., severe asthma, chronic obstructive pulmonary disease, emphysema), or orthopedic limitations (e.g., foot, knee, or hip problems) that would result in bodily injury or limit performance. A modified version of the Physical Activity Readiness Questionnaire (PAR-Q) was used to screen participants prior to participation in the study. Additionally, physician clearance was obtained for each participant.

Echocardiography

A limited study transthoracic echocardiogram was obtained on each participant adhering to American Society of Echocardiography (ASE) criteria (Mor-Avi et al., 2011). Echocardiography was performed with a commercially available scanner (IE33, Phillips) and transducer. Imaging data was acquired by two level 2 echo trained cardiovascular physicians who were part of the study team. Several consecutive cardiac cycles were stored for later post-processing on an external workstation by the same two physicians. Two-dimensional global longitudinal strain (speckle-tracking) was calculated using dedicated software (QLAB, Phillips). Since GLS quantifies left ventricular myocardial shortening during systole, lower more negative values represent superior myocardial mechanics. To render GLS–CBF and GLS–$fitness_{CR}$ relationships more interpretable, participant's GLS values were multiplied by −1 so that higher scores reflect superior myocardial shortening mechanics.

Cardiorespiratory fitness assessment

All participants completed a physician-supervised maximal graded exercise test (Max GXT) to assess VO_2 peak using a previously described standardized protocol (Johnson et al., 2012). Briefly, the exercise test was conducted in the Assessment Laboratory of the University of Kentucky's Center for Clinical and Translational Sciences Translation Analytic and Assessment Core using an indirect calorimetry system with integrated 12-lead ECG (Sensormedics Vmax229 metabolic cart; Yorba Linda, CA). A multistage stepwise treadmill protocol, including 3-minute stages, was used to assess $fitness_{CR}$.

During the Max GXT continuous heart rate and dynamic heart function were measured and monitored via 12-lead ECG. Oxygen consumption was measured breath-by-breath and later averaged over one minute intervals and expressed relative to body weight (ml/kg/min) during the test and recovery period. Manual blood pressures and rating of perceived exertion (RPE; using the modified Borg Scales) were collected during the final 30 s of each 3-minute stage. All tests were terminated upon participant reported volitional fatigue, the presence of any absolute or relative indications for terminating exercise testing in accordance with the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (Thompson et al., 2010), or any symptom the supervising physician considered hazardous to the well-being of the participant. All exercise tests were performed within 23 days of the acquisition of the MRI (mean = 10.4, SD = 4.9).

VO_2 peak was defined as meeting >2 of the following 3 criteria: 1) achievement of an age-predicted maximum HR; 2) self-reported RPE scores > 17; and 3) a respiratory exchange ratio of > 1.1. Additionally, the highest observed VO_2 value was used for all analyses. The standard 220-age equation was used to calculate age-predicted maximum HR. Five participants were not included in the analysis because they failed to meet >2 of the 3 criteria.

The primary purpose of the study was to characterize the relationship between myocardial function, $fitness_{CR}$, and cerebral blood flow. We used a modified version of our previously constructed composite score (see Johnson et al., 2012) which includes total time on treadmill (seconds) and VO_2 peak, two $fitness_{CR}$ metrics shown to be predictive of WM microstructure (Johnson et al., 2012), to generate a score representative of $fitness_{CR}$. Briefly, values for VO_2 peak and total time on treadmill were normalized across each aerobic $fitness_{CR}$ metric [e.g., normalized value $A = (A - min) / (max - min)$; range from 0 to 1 for each metric] and then summed to create a single value between 0 and 2 (i.e., composite-$fitness_{CR}$). Values closer to 0 represent those participants with lower $fitness_{CR}$ levels and values closer to 2 represent those participants with higher $fitness_{CR}$ levels.

MRI acquisition

Data were collected on a 3 Tesla Siemens TIM scanner at the University of Kentucky. A 32-channel imaging coil was used. Three primary imaging sequences were collected for each participant in this study: 1) a high-resolution, T1-weighted sequence for subsequent localization of cerebral blood flow and resting-state activity in standard stereotactic space; 2) T2*-weighted images sensitive to resting fluctuations in BOLD signal; and 3) a Pulsed ASL (PASL) sequence for estimation of absolute cerebral blood flow.

Two high-resolution, 3D anatomic images were acquired using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: echo time (TE) 2.26 ms, repetition time (TR) 2530 ms, field of view (FOV) of 256 mm, flip angle (FA) of 7°, and voxel size of 1 × 1 × 1 mm. CBF was estimated using a PASL sequence with a proximal inversion with a control for off-resonance effects (PICORE) and quantitative imaging of perfusion with a single subtraction and thin-slice T_{I1} (700 ms) periodic saturation (Q2TIPS) sequence. One hundred and four images were acquired with $T_{I2} = 1900$ ms, TE = 12 ms, TR = 3400 ms, FA = 90°, FOV = 256 mm, 64 × 64 matrix, and voxel size of 4.0 × 4.0 × 5.0 mm. Tag and untagged image pairs were acquired in order to calculate CBF in each voxel. A single M_0 image was also acquired (total images collected = 105) prior to steady state. Finally, T2*-weighted images sensitive to changes in BOLD were acquired with the following parameters: TE 30 ms, TR 2000 ms, FOV = 224 mm, (FA) of 76°, and voxel size of 3.5^3 mm^3.