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Effects of cardiorespiratory fitness and cerebral blood flow on cognitive outcomes in older women

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Abstract

The mechanisms by which aerobic fitness confers beneficial effects on cognition with aging are unclear but may involve cerebrovascular adaptations. In a cross-sectional study of women from the community ($n = 42$; age range = 50–90 years), we sought to determine whether physical fitness is associated with higher cerebrovascular function, and its relationship to cognition. Main outcome measures included resting cerebral blood flow, cerebrovascular reserve, physical fitness (i.e., $\dot{V}O_2$max) and cognition. Physically fit women had lower resting mean arterial pressure (MAP) and higher cerebrovascular conductance (CVC) than sedentary women. Overall cognition was negatively correlated with age and positively correlated with $\dot{V}O_2$max. $\dot{V}O_2$max was a predictor of resting CVC and MAP, and CVC and MAP when end-tidal gases were held constant at near-resting values. MAP and CVC were predictors of cognition. This study identified strong associations between physical fitness, vascular function and cognition, and provides new understanding regarding the mechanisms by which fitness positively impacts cognition with aging. The implications of this research are considerable and warrant future investigation.

Keywords: Cerebrovascular circulation; Women; Hypertension; Transcranial Doppler ultrasound; Aging; Exercise; Cognitive function

1. Introduction

The cresting of the wave of baby boomers begins in 2011 as the first of the *Silver Tsunami* have their 65th birthdays, which will lead to a doubling of the proportion of the population over 65 years in the ensuing 25 years. Women over the age of 80 are the fastest growing sub-group of this population. Many believe that they can expect to live the majority of their remaining years with moderate or severe dependence because of various chronic diseases. Furthermore, cognitive decline and dementia will reach epidemic proportions in western countries. The link between cerebrovascular disease and clinical dementia has been strongly supported by findings from the Nun study (Snowdon et al., 1997), which reported that patients with pathological findings of Alzheimer's dementia have a much greater chance of showing clinical dementia if they have concurrent cerebral infarcts. Indeed, it is estimated that 5% of all persons age 65

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and older have vascular cognitive impairment (Rockwood et al., 2000).

The notion that physical activity affects cognitive performance has been investigated for over 30 years (Diesfeldt and Diesfeldt-Groenendijk, 1977). However, despite the literature showing that physical activity has a favorable effect on cognition in older populations, the underlying mechanisms remain unknown. This important knowledge gap was recognized in the recent document a *National Public Health Road Map to Maintaining Cognitive Health* (CDCPAA, 2007) that included several recommendations about the need to understand the mechanisms by which physical activity promotes vascular and cognitive health.

Aging is associated with a progressive decline in baseline cerebral blood flow that differs in men and women (Strandgaard, 1993; Yonas et al., 1993). In pre-menopausal women, the decline in cerebral blood flow with age is less pronounced than in men but is accelerated after menopause and persists into old age (Matteis et al., 1998). This biphasic phenomenon of cerebral blood flow changes in women might be explained by the beneficial effects of ovarian hormone modulation of cerebral blood flow before menopause, followed by a predominant influence of other factors thereafter.

Aging is also associated with a decline in cognitive function and is associated with Alzheimer's disease and vascular dementia (Albert et al., 1995). Physical inactivity is a modifiable risk factor for stroke (Gorelick et al., 1999; Rossouw et al., 2002). Conversely, physical activity has been shown to correlate with greater maintenance of cognitive ability, particularly executive control functions, with age (Kramer et al., 2003). More recently, cardiorespiratory fitness has been found to be associated with reduced brain atrophy in Alzheimer's disease (Burns et al., 2008). However, the mechanisms whereby physical activity exerts a beneficial effect on the cerebral circulation and on cognition remain to be defined. Although little is known about the mechanisms of regulation in older humans, a recent study in young adults (Pereira et al., 2007) and recent studies in animals have provided compelling evidence for the role of vascular adaptations including angiogenesis (Black et al., 1990; Churchill et al., 2002), and the possible involvement of neurogenesis and synaptogenesis (Black et al., 1990; Pereira et al., 2007; Swain et al., 2003).

In a 4-year prospective longitudinal study, it was found that those individuals who were physically inactive in the first 4 years of retirement showed significant declines in cerebral perfusion and general cognition while those individuals who continued to work or who were physically active maintained perfusion and general cognition (Rogers et al., 1990). However, the relation between cognitive function and changes in cerebrovascular reserve with age and physical fitness has not previously been investigated. We tested the hypotheses that being physically active would be associated with greater retention of cognitive function and cerebrovascular reserve than being sedentary, and that the relation between fitness and cognition has a vascular basis.

2. Methods

A cross-sectional study design with detailed physiological assessment was used. Postmenopausal women aged 50–90 years were identified in the community through advertisements at the University of Calgary, Calgary Health Region, and in the general community. Eligibility criteria included: non-smokers, ability to perform moderate exercise, body mass index (BMI) $\leq$30 kg/m^2 (thus, avoiding co-morbidities associated with obesity), normal spirometry, less than 20% stenoses of the carotid arteries, and no evidence of significant co-morbid disease or pharmacologic therapies, as determined by the study physician, that would interfere with their ability to exercise or with study outcomes. Specific exclusion criteria included heart and/or chest pains upon physical exertion; fainting spells/dizziness; recent surgery or major trauma (<6 months); known asthma or sleep apnea; history of myocardial infarction, angina, arrhythmias, valve disease, chronic heart failure, stroke, cardiovascular or cerebrovascular disease, chronic headache or migraine, blood clots/thrombosis; prescription medications including beta-blockers, anti-depressants, digitalis/digoxin, blood thinners (e.g., Warfarin), tamoxifen, evista (raloxifene), corticosteroids (e.g., prednisone), adrenaline/epinephrine and anti-arrhythmics (e.g., Norpace).

The study requirements were fully explained to each subject, and written informed consent was obtained. The study protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary.

We determined maximal oxygen uptake (VO_2max), indices of resting cerebral blood flow, isocapnic cerebral blood flow (a test to assess cerebrovascular reserve) and cerebral blood flow response to a vascular reactivity test (i.e., response to CO_2) and to sub-maximal exercise, and evaluated cognitive function. The cognitive function assessments and analyses were completed by an assessor blinded to the fitness status of the study subjects.

Subjects completed four visits, and refrained from eating or drinking any caffeine-containing beverages for at least 4 h prior to each of the physiological testing sessions. The first visit was a screening session and involved: (i) collecting participant demographic data, (ii) anthropometric measurements including measurements of height, weight, hip-to-waist ratio and body fat assessment by measuring subcutaneous adipose tissue on four sites using a Harpenden skin fold caliper and the Durnin–Womersley Method (Durnin and Womersley, 1974), (iii) completion of a lifestyle questionnaire adapted from the *Past Year Total Physical Activity Questionnaire* (Friedenreich et al., 1998, 2006) from which hours of recreational, volunteer, and household activities were summed and converted to metabolic equivalents (METs) using the Physical Activity Compendium (Ainsworth et al., 1993, 2000), (iv) spirometry testing and (v) a carotid artery ultrasound screening.

Carotid screening was carried out in all women. A high-resolution ultrasound system (Hewlett Packard Sonos 5500, Palo Alto, CA, USA) was used with a 7.5 MHz linear array