Elevated Aerobic Fitness Sustained Throughout the Adult Lifespan Is Associated With Improved Cerebral Hemodynamics

Damian M. Bailey, PhD, FPVRI, FRSC, FACSM*; Christopher J. Marley, MPhil*; Julien V. Brugniaux, PhD; Danielle Hodson, MPhil; Karl J. New, PhD; Shigehiko Ogoh, PhD; Philip N. Ainslie, PhD*

**Background and Purpose**—Age-related impairments in cerebral blood flow and cerebrovascular reactivity to carbon dioxide (CVRCO₂) are established risk factors for stroke that respond favorably to aerobic training. The present study examined to what extent cerebral hemodynamics are improved when training is sustained throughout the adult lifespan.

**Methods**—Eighty-one healthy males were prospectively assigned to 1 of 4 groups based on their age (young, ≤ 30 years versus old, ≥ 60 years) and lifetime physical activity levels (trained, ≥ 150 minutes recreational aerobic activity/week versus sedentary, no activity). Middle cerebral artery blood velocity (MCAv, transcranial Doppler ultrasound), mean arterial pressure (MAP, finger photoplethysmography), and end-tidal partial pressure of carbon dioxide (PETCO₂, capnography) were recorded during normocapnia and 3 mins of iso-oxy hypercapnea (5% CO₂). Cerebrovascular resistance/conductance indices (CVRi/CV Ci) were calculated as MAP/MCAv and MCAv/MAP, respectively, and CVRCO₂ as the percentage increase in MCAv from baseline per millimeter of mercury (mm Hg) increase in PETCO₂. Maximal oxygen consumption (VO₂MAX, online respiratory gas analysis) was determined during cycling ergometry.

**Results**—By design, older participants were active for longer (49±5 versus 6±4 years, P<0.05). Physical activity attenuated the age-related declines in VO₂MAX, MCAv, CV Ci, and CVRCO₂ and increase in CVRi (P<0.05 versus sedentary). Linear relationships were observed between VO₂MAX and both MCAv and CVRCO₂ (r = 0.58–0.77, P<0.05).

**Conclusions**—These findings highlight the importance of maintaining aerobic fitness throughout the lifespan given its capacity to improve cerebral hemodynamics in later-life. (Stroke. 2013;44:00-00.)

**Key Words:** aerobic exercise ▪ aging ▪ cerebrovascular circulation ▪ perfusion ▪ stroke

Sedentary aging is associated with a longitudinal decline in cerebral blood flow (CBF) and cerebrovascular reactivity to carbon dioxide (CVRCO₂), impairments that increase the risk of cognitive decline, dementia, and stroke in either healthy or diseased populations. Given that curative treatments are currently unavailable, major efforts have focused on prevention including modifiable risk factors such as physical activity.

However, to what extent lifelong physical activity impacts CVRCO₂ remains to be established despite short-term improvements that have been observed after 3 to 6 months of exercise training in healthy adults and stroke survivors. To address this and extend earlier work, we compared both CBF and CVRCO₂ across the extremes of aging and physical activity in a select sample of healthy males to confirm whether these hemodynamic indices are indeed positively associated with VO₂MAX.

**Materials and Methods**

**Participants**

**Recruitment**

After ethical approval and written informed consent, we recruited both young (aged ≤ 30 years) and old (≥ 60 years) males who according to self-report lifetime physical activity levels were either trained (≥ 150 minutes of moderate to vigorous intensity recreational aerobic activity/week) or sedentary throughout the adult lifespan consistent with...
current recommendations) or sedentary (no formal recreational activity outside of everyday living). We specifically chose to exclude females given our inability to control for differences in estrogen levels (during the menstrual cycle, menopause, and hormone replacement therapy), which has been shown to cause intracranial vasodilatation and increase CBF.

**Screening**

All potential participants were subject to a detailed clinical examination that included a 12-lead ECG. They were included if they were nonsmokers, nonobese (body mass index <30 kg/m²), and free of any cardiovascular (eg, type 2 diabetes mellitus, coagulopathy, hypertension), cerebrovascular (eg, stroke, transient ischemic attack, migraine), or respiratory (eg, asthma, chronic obstructive pulmonary disorder) diseases. Participants were also screened for any psychiatric or neurological disorders, including dementia and depression and were not prescribed any medications.

**Assignment**

Eighty-one males were considered eligible for the study. They were prospectively assigned to 1 of 4 groups based on their age and physical activity levels and included the following: young sedentary (n = 19), young trained (n = 20), old sedentary (n = 19), and old trained (n = 23). Every attempt was made to match the trained groups for (weekly) exercise duration, frequency, and intensity.

**Experimental Procedures**

**Cerebral Hemodynamics: CBF, MAP, and CVR\textsubscript{CO\textsubscript{2}}**

The middle cerebral artery (MCA) was insonated using 2 MHz pulsed transcranial Doppler ultrasound (Multi-Dop X4, DWL Elektronische Systeme GmbH, Sipplingen, Germany) and mean arterial pressure (MAP) determined by finger photoplethysmography (Finometer PRO, Finapres Medical Systems, Amsterdam, The Netherlands). Data were sampled continuously at 1 kHz and stored for off-line analysis. Cerebrovascular resistance and conductance indices (CVRi and CVCi) were calculated as MAP/MCAv and MCAv/MAP respectively. CVR\textsubscript{CO\textsubscript{2}} was calculated as the percentage increase in MCAv from baseline per mm Hg increase in PET\textsubscript{CO\textsubscript{2}}, determined by capnography (ML 206, ADInstruments Ltd, Oxford, UK) in response to 3 minutes breathing 5% CO\textsubscript{2} (balanced air).

**Cardiorespiratory Fitness**

Maximal oxygen consumption (VO\textsubscript{MAX}) was determined during an incremental cycling test to volitional exhaustion. Expired gas fractions were determined online (MedGraphics, Ultima Series) and VO\textsubscript{MAX} confirmed according to established criteria.

**Statistics**

After confirmation of distribution normality using Shapiro–Wilk W tests, between group differences were analyzed using a 2-way (age, young versus old × status, sedentary versus trained) factorial analysis of variance (ANOVA). After an interaction effect, differences were located using a 1-way ANOVA and post hoc Tukey tests. Relationships were determined using Pearson Product Moment Correlations. Significance was established at \(P<0.05\) and data expressed as mean±SD.

**Results**

By design, old participants were physically active for longer than the young (49±5 versus 6±4 years, \(P<0.05\)). Aging was associated with a lower VO\textsubscript{MAX}, MCAv, CVCi, and CVR\textsubscript{CO\textsubscript{2}}, and elevations in body mass index and CVRi, whereas MAP remained unchanged (Table). Physical activity was associated with an elevation in VO\textsubscript{MAX} and corresponding improvement in cerebral hemodynamics. Indeed, positive linear relationships were observed between VO\textsubscript{MAX} and both MCAv and CVR\textsubscript{CO\textsubscript{2}} (pooled sedentary and trained data sets) in both young and old participants (Figure, A–D). Furthermore, at an approximate average MCAv of 50 cm/s and CVR\textsubscript{CO\textsubscript{2}} of 2%/mm Hg, the difference between trained and sedentary participants equated to ≈11- and 18-year reduction, respectively in the brain’s hemodynamic age. In contrast, physical activity did not alter the age-related rate of decline in MCAv (sedentary, –0.3 cm/s/year versus trained, –0.4 cm/s/year; \(P>0.05\)) or CVR\textsubscript{CO\textsubscript{2}} (sedentary, –0.02%/mm Hg/year versus trained, –0.02%/mm Hg/year; \(P>0.05\)).

**Discussion**

The major finding of the present study is that elevated cardiorespiratory fitness was shown to attenuate the age-related decline in cerebrovascular hemodynamics given its association with improved cerebral perfusion and CO\textsubscript{2} vasoreactivity. This highlights the neuroprotective benefits of active living given its capacity to improve cerebral hemodynamics throughout the adult lifespan.

To our knowledge, this is the first cross-sectional study to assess the association between aerobic fitness and both MCAv and CVR\textsubscript{CO\textsubscript{2}} across the extremes of healthy human aging. Our findings confirm the age-related decline in MCAv originally documented by Ainslie et al\textsuperscript{1} and corresponding increase incurred through regular exercise training. Indeed, when comparing the two extremes of chronological age, physical activity was shown to reduce the brain’s hemodynamic age by more than a decade, which is in agreement with previous estimates.\textsuperscript{1}

Our study extends these original works by further documenting exercise-induced improvements in CVR\textsubscript{CO\textsubscript{2}}, which seemed to be even more marked with physical activity conferring ≈18-year reduction in the brain’s functional age. These findings are in agreement with another transcranial Doppler–based study,\textsuperscript{2} though in conflict with recent MRI-based studies focused on regional as opposed to global cerebral perfusion that have used alternative hypercapnic challenges.\textsuperscript{12,13} Furthermore, the consistent relationships observed between VO\textsubscript{MAX} and both MCAv and CVR\textsubscript{CO\textsubscript{2}} confirm that the benefits of aerobic exercise are not simply confined to the cardiovascular circulation but can equally extend to the cerebrovasculature. This was clearly evident in later-life, indicating that the human brain retains a life-long capacity for exercise adaptation further justifying exercise prescription in the elderly.

The present findings need to be interpreted with a degree of caution given some experimental limitations. A cross-sectional design cannot establish causality and also relies on self-report approaches when recalling lifelong participation in physical activity.\textsuperscript{14} However, we sought to minimize this potential confound through the combined use of a validated physical activity questionnaire\textsuperscript{9} and direct measurement of cardiorespiratory fitness. Furthermore, we did not explore the molecular mechanisms underlying enhanced neuroplasticity such as exercise-induced increases in the vascular bioavailability of nitric oxide, brain-derived neurotrophic factor, and insulin-like growth factor.\textsuperscript{1,3,7} Likewise, it remains unclear whether these hemodynamic adaptations would have translated into improved cognitive function and stroke risk in later-life as previously suggested,\textsuperscript{3,5} which would have placed our findings into clearer clinical context.
Rigorous inclusion criteria meant that we were only able to recruit relatively small sample sizes into each group. However, retrospective power analysis revealed that we were adequately powered to detect main effects with values exceeding 0.90 for all dependent variables examined. Furthermore, given that our study was exclusively restricted to males, it would be of future interest to determine whether physical activity has an equivalent impact on females given the known sex differences in baseline cerebral hemodynamics to make our findings more applicable to the general population. Finally, we relied on transcranial Doppler measurements of blood flow velocity as an indirect surrogate of global CBF, a limitation that is well established though MCAv is considered a reliable indicator of cerebral perfusion both at rest and when assessing the dynamic response to hypercapnia.

In conclusion, the present findings highlight the importance of being physically active and maintaining aerobic fitness throughout the lifespan given the improvements observed in cerebrovascular hemodynamics. Larger-scale, longer-term, mixed-sex, interventional studies are warranted to confirm the findings on a more generalizable population. The Table below presents the participant demographics of our study.

### Table. Participant Demographics

<table>
<thead>
<tr>
<th>Activity</th>
<th>Age, y</th>
<th>BMI, kg m⁻²</th>
<th>VO₂max, L min⁻¹</th>
<th>VO₂max, mL kg⁻¹min⁻¹</th>
<th>MCAv, cm s⁻¹</th>
<th>MAP, mm Hg</th>
<th>CVRi, mm Hg cm⁻¹s⁻¹</th>
<th>CVRCO₂ (%·mm Hg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>Young</td>
<td>25±5</td>
<td>26.2±2.9</td>
<td>3.05±0.52</td>
<td>36±5</td>
<td>52±11</td>
<td>0.60±0.16</td>
<td>2.10±0.73</td>
</tr>
<tr>
<td>Trained</td>
<td>Old</td>
<td>23±4</td>
<td>23.9±2.7</td>
<td>4.75±0.73</td>
<td>62±9*</td>
<td>64±13</td>
<td>0.76±0.19</td>
<td>3.78±0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.77±0.25*†</td>
<td>24±4†</td>
<td>37±8</td>
<td>2.45±0.46</td>
<td>1.45±0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.77±0.45*†</td>
<td>39±6†</td>
<td>46±11</td>
<td>2.02±0.56</td>
<td>2.88±1.03</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CVR/CVC/CVRCO₂, cerebrovascular resistance/conductance indices/reactivity to carbon dioxide; MAP, mean arterial pressure; MCAv, middle cerebral artery velocity; and VO₂max, maximal oxygen uptake.

*=†Difference within/between age groups (P<0.05).

Figure. Relationships between cardiorespiratory fitness and cerebrovascular hemodynamics in young (A and B) and old (C and D) adults as a function of physical activity status. CVR CO₂ indicates cerebrovascular reactivity to carbon dioxide; MCAv, middle cerebral artery velocity; and VO₂max indicates maximal oxygen uptake.
our findings and further explore the mechanistic bases underlying the neuroprotective benefits of physical activity.

Sources of Funding
Funding was provided by the John Peter Rhys Williams Trust (to D.M.B.).

Disclosures
None.

References
Elevated Aerobic Fitness Sustained Throughout the Adult Lifespan Is Associated With Improved Cerebral Hemodynamics

Damian M. Bailey, Christopher J. Marley, Julien V. Brugniaux, Danielle Hodson, Karl J. New, Shigehiko Ogoh and Philip N. Ainslie

*Stroke*. published online August 20, 2013;

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2013/08/20/STROKEAHA.113.002589