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Wheeler, M. J., Dunstan, D. W., Smith, B., Smith, K. J., Scheer, A., Lewis, J., Naylor, L. H., Heinonen, I., Ellis, K. A., Cerin, E., Ainslie, P. N. and Green, D. J. (2019). Morning exercise mitigates the impact of prolonged sitting on cerebral blood flow in older adults. *Journal of Applied Physiology*, 126(4), pp. 1049-1055. https://doi.org/10.1152/japplphysiol.00001.2019

Morning exercise mitigates the impact of prolonged sitting on cerebral blood flow in older adults

Michael J Wheeler[1,2], David W Dunstan[1,2,9], Brianne Smith[1], Kurt Smith[1,3], Anna Scheer[4], Jaye Lewis[1], Louise Naylor[1], Ilkka Heinonen[5,6], Kathryn A Ellis[7], Ester Cerin[2,8,9], Philip N Ainslie[10], Daniel J Green[1]

[1] School of Human Sciences (Exercise and Sport Science), The University of Western Australia, Perth WA, Australia

[2] Baker Heart and Diabetes Institute, Melbourne VIC, Australia

[3] School of Kinesiology, Lakehead University, Thunderbay ONT, Canada

[4] School of Physiotherapy and Exercise Science, Faculty of Health Science, Curtin University, Perth WA, Australia

[5] Turku PET Centre, University of Turku, Finland

[6] Rydberg Laboratory of Applied Sciences, ETN, Halmstad University, Sweden

[7] Department of Psychiatry, University of Melbourne, Parkville, Melbourne VIC, Australia

[8] School of Public Health, The University of Hong Kong

[9] Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne VIC, Australia

[10] School of Health and Exercise Sciences, The University of British Columbia, Canada

Running Head: Exercise improves the pattern of cerebral blood flow

Corresponding author:

Michael J Wheeler

Baker Heart and Diabetes Institute

99 Commercial Rd., Melbourne, Victoria, 3004, Australia

Phone: +61 3 8532 1898 Fax: +61 3 8532 1100

Email: michael.wheeler@baker.edu.au

Twitter: @_michaelwheeler

Tables and figures: 4 figures, 1 table

ABSTRACT

Preventing declines in cerebral blood flow is important for maintaining optimal brain health with aging. We compared the effects of a morning bout of moderate-intensity exercise, with and without subsequent light-intensity walking breaks from sitting, on cerebral blood velocity over 8-hours in older adults. In a randomized crossover trial, overweight/obese older adults (n=12, 2♀, 70±7 years; 30.4±4.3 kg/m^2), completed 3 acute conditions (6-day washout); SIT: prolonged sitting (8hr, control); EX+SIT: sitting (1hr), moderate-intensity walking (30min), followed by uninterrupted sitting (6.5hr); EX+BR: sitting (1hr), moderate-intensity walking (30min), followed by sitting (6.5hr) interrupted with 3 minutes of light-intensity walking every 30 minutes. Bilateral middle cerebral artery velocities (MCA*v*) were determined using transcranial Doppler at 13 time points across the day. The temporal pattern and average MCA*v* over 8-hours was determined. The pattern of MCA*v* over 8-hours was a negative linear trend in SIT ($p<0.001$), but a positive quadratic trend in EX+SIT ($p<0.001$) and EX+BR ($p<0.01$). Afternoon time points in SIT were lower than baseline within condition ($p\leq0.001$ for all). A morning dip in MCA*v* was observed in EX+SIT and EX+BR ($p<0.05$ relative to baseline), but afternoon time points were not significantly lower than baseline. The average MCA*v* over 8-hours was higher in EX+SIT than SIT ($p=0.007$) or EX+BR ($p=0.024$). Uninterrupted sitting should be avoided, and moderate-intensity exercise should be encouraged for the daily maintenance of cerebral blood flow in older adults. The clinical implications of maintaining adequate cerebral blood flow include the delivery of vital oxygen and nutrients to the brain.

NEW & NOTEWORTHY

This is the first study to measure the combined effects of an exercise bout with breaks in sitting on cerebral blood velocity in older adults. Using frequent recordings over an 8-hour period, we have performed a novel analysis of the pattern of cerebral blood velocity, adjusting for concurrent measures of mean arterial pressure and other potential confounders in a linear mixed effects regression.

Keywords

Acute exercise, sedentary behavior, transcranial Doppler, older adults, brain health

INTRODUCTION

The prevalence of stroke and dementia is increasing due to population aging (14). Aging is also associated with an increased prevalence of cardiovascular risk factors for cerebrovascular disease such as physical inactivity, obesity, hypertension, hyperlipidaemia and dysglycemia (43). Therefore, strategies to maintain cerebrovascular health among older adults with cardiovascular risk factors are a public health priority. Evidence demonstrates that exercise in particular is associated with a reduced incidence of stroke (24, 39), and may also delay the progression of dementia (19, 25). However, the mechanisms underlying these benefits in humans remain unclear. Whilst exercise may exert some of its cardiovascular effects by modifying traditional risk factors (18, 22), there are also direct benefits of exercise on arterial function and health (17, 37). In addition, regular exercise can mitigate the decline in cerebral blood flow associated with ageing (1). Insight from animal studies demonstrates the importance of exercise-induced increases in cerebral blood flow for neurogenesis, cerebral angiogenesis and related growth factors (3, 28, 30, 35). In order to understand cerebrovascular regulation in response to exercise in humans, many studies focus on cerebral blood flow during or immediately after exercise (27). However, few experiments have characterized the cerebral blood flow response to different patterns of physical activity over the whole day, an imperative for the design of optimal exercise interventions.

Over a whole waking day, older adults spend about 5% of time engaged in exercise of moderate-to-vigorous intensity, but spend a majority of time in sedentary behavior which carries an increased risk for all-cause mortality (15, 20, 21). Recent evidence suggests that sedentary behaviors such as prolonged sitting may be negatively associated with aspects of brain health such as cognitive function and medial temporal lobe thickness (13, 33). In addition, laboratory studies which have investigated reducing and breaking up sitting with

intermittent physical activity have reported beneficial impacts on multiple systems relevant to brain health, including carbohydrate and lipid metabolism (4, 16), blood pressure (5, 10), sympathetic function (10) and vascular function (7, 32, 36). In response to accumulating evidence, some government guidelines now recommend reducing sitting in addition to engaging in moderate-to-vigorous intensity exercise (2, 11). In the US, the scientific report which informed the *2018 Physical Activity Guidelines for Americans* highlighted a need for future studies to investigate different patterns of physical activity and sedentary behavior on brain health outcomes (29). However, it is currently unknown whether engaging in moderate-to-vigorous intensity exercise would mitigate any potential decline in cerebral blood flow during a subsequent period of prolonged sitting. It is also unknown whether combining a bout of moderate-to-vigorous exercise with subsequent breaks in sitting would further enhance the cerebral blood flow response.

The aim of this study was to assess the impact of a moderate-intensity exercise bout, with or without subsequent breaks in sitting, on middle cerebral artery blood velocity (MCA*v*) in older adults. We hypothesized that an acute bout of exercise would enhance cerebrovascular responses over an eight hour period, relative to prolonged uninterrupted sitting. In addition, we hypothesized that cerebrovascular responses following acute exercise would be further enhanced by subsequent exposure to breaks in sitting.

MATERIALS AND METHODS

This experiment is a sub-study of a larger randomized crossover trial (ACTRN12614000737639) and the detailed methods have been published independently (12).

Participants

Men and postmenopausal women (n=12, 2♀, age ≥ 55 to ≤ 80 years; BMI ≥ 25 kg/m^2 to < 45 kg/m^2; English-speaking) were recruited from the local community via advertisement in Perth, Western Australia. Full participant characteristics are found in Table 1. This study was approved by the Human Research Ethics Committee of The University of Western Australia (RA/4/1/6990). Participants provided written informed consent prior to testing. All participants were screened for cardiovascular risk and previous cardiovascular events. Exclusion criteria included self-reported sitting < 5 hours per day, self-reported engagement in moderate-intensity exercise ≥ 150 min/week for > 3 months, probable dementia (Telephone Interview of Cognitive Status score of < 19), cognitive impairment (Mini Mental State Exam < 24), depressive symptoms of clinical relevance (Geriatric Depression Score > 6 or Hospital Anxiety and Depression Scale score – depression score >8), diagnosed diabetes, use of glucose/lipid lowering medication, antidepressant medications, beta blockers, anti-anxiety medication, excessive alcohol consumption (> 8 points on the Alcohol Use Disorders Identification Test), abnormal ECG (determined by study doctor), high resting blood pressure (office systolic > 160 mm Hg or diastolic >100 mm Hg), or major illness/physical problems (acute or chronic) that would limit ability to perform moderate-intensity exercise.

Study Design

Participants were randomized to participate in three laboratory sessions, separated by a minimum of six days (Figure 1). The order of conditions was block randomized and stratified by sex by an independent third party using a computer-generated random sequence and stored in sealed envelopes as previously outlined (12). Researchers were blinded to the order of conditions until familiarisation was complete and participants were blinded to the conditions

until each day of testing. Experimental conditions included: *Sitting (SIT)*: uninterrupted sitting (8hr, control); *Exercise + Sitting (EX+SIT)*: sitting (1hr), moderate-intensity treadmill walking (30min) followed by uninterrupted sitting (6.5hr); *Exercise + Breaks (EX+BR)*: sitting (1hr), moderate-intensity treadmill walking (30min) followed by sitting (6.5hr) interrupted every 30 minutes with 3 minutes of light-intensity treadmill walking. A familiarisation session was completed three to five days prior to testing, in which participants were familiarized with all testing equipment and procedures, including treadmill walking. During the 48 hours prior to testing, participants were instructed to avoid caffeine, alcohol and moderate-to-vigorous physical activity. In addition, food was controlled from the night before testing where participants consumed a standardized dinner at home between 7pm and 9pm in place of their regular dinner. This meal was tailored for each participant to meet 33% of estimated daily energy requirement with a macronutrient profile of 55–58% carbohydrate, 29–31% fat and 12–15% protein as previously described (12).

Insert figure 1 about here

Exercise

The moderate-intensity exercise bout was performed on a treadmill at the same predetermined speed and incline for both EX+SIT and EX+BR. The speed was set at 3.2km·h^{-1} and the incline was tailored for each participant during the familiarization session to induce a heart rate indicative of moderate-intensity, defined as 65% to 75% of age predicted maximum heart rate. Each three-minute light-intensity walking break performed during EX+BR was completed on a treadmill with 0% incline at a speed of 3.2km·h^{-1}, which was a walking speed for all participants. Heart rate (Polar Electro, Kempele, Finland) and ratings of perceived exertion (RPE scale 6-20; light intensity 9-11 RPE; moderate-intensity

12-15 RPE) were collected at 5-minute intervals during the 30-minute bout of exercise and at the end of each three-minute walking break.

Experimental day protocol

Participants reported to the laboratory at ~7am following an overnight fast (>10 hours). Participants remained seated while equipment was set up and the bilateral middle cerebral arteries were located as detailed below, prior to the start of the experiment at ~8am (0 hour). The experiment began with baseline recordings of MCA*v*, blood pressure and heart rate which were obtained prior to the administration of a standardized breakfast meal. Breakfast and lunch were administered at 40 and 280 minutes into the experiment and were consumed over a 20 minute period. All meals were standardized according the same criteria as the evening meal and remained the same for a given participant during all conditions. After breakfast the protocol was followed according to randomization and participants were instructed to remain seated apart from leaving the chair to void or to perform predetermined treadmill walking in the EX+SIT and EX+BR conditions. Study outcomes were measured at multiple time points across the day (Figure 1). All measures of MCA*v* were taken during steady state sitting periods, such that in the EX+BR condition measures were collected at least 25 minutes after the most recent activity break.

Cerebrovascular function

Cerebral blood flow was indexed using transcranial Doppler (TCD; Spencer Technologies, Seattle, WA). Bilateral measures of middle cerebral artery velocity (MCA*v*) were determined with a 2MHz probe transfixed to the posterior aspect of the temporal window of the skull using the Mark 600 headframe (Spencer technologies, Seattle, USA). The headframe was

188 secured in place to negate movement effects on the insonation site and participants remained
189 instrumented for the entire experiment to avoid relocating the MCA. The location of the
190 middle cerebral artery was determined by locating the trifurcation of the circle of Willis (~45-
191 65 mm) in the anterior circulation of the brain, as previously outlined (42). The MCA*v* was
192 continuously sampled for 5 minutes at baseline and for 30 seconds during subsequent time
193 points, at 1000Hz via an analogue-to-digital converter (Powerlab, 16/30 AD Instruments,
194 Colorado Springs, CO, USA). Data were analyzed offline using a specialized analytical
195 software package (LabChart 8, AD Instruments, Colorado Springs, CO, USA). The sum of
196 bilateral velocities was calculated for statistical analyses. The sum of bilateral velocities
197 represents a surrogate measure of the total amount of blood being delivered to the brain.
198 Summing the bilateral velocities also accounts for expected anatomical differences between
199 the left and right MCA, detection of which would be diminished by averaging the bilateral
200 velocities.
201
202
203 *Assessment of hemodynamic variables*
204 Resting blood pressure and heart rate were measured in a seated position. A
205 photoplethysmographic method was used for serial BP assessment (Finometer Pro, Finapres
206 Medical Systems, Amsterdam, the Netherlands) and this was calibrated against automated
207 brachial oscillometry (HEM-907, Omron, Kyoto, Japan). In all conditions, blood pressure and
208 heart rate were measured contemporaneously with MCA*v*, and at a time consistent with the
209 period immediately preceding the 3-minute walking break during the EX+BR condition.
210

Statistical analysis

Based on previous evidence we estimated the effect size (Cohen's d for repeated measures) of exposure to intermittent light-intensity walking breaks relative to uninterrupted sitting, to be ~1.1 for MCA*v* (6). Assuming a within participant correlation of 0.6, the effective sample size to detect this difference with a power of 0.80 and a two tailed probability of 0.05, is 9 participants. The order of conditions was block randomized and stratified by sex by an independent third party using a computer generated random sequence and stored in sealed envelopes as previously outlined (12). Analysis was performed by technicians blinded to the study conditions. Following recent recommendations on data analysis of cross-over trials (23), generalized linear mixed models with random intercepts were used to evaluate the differential effects of the experimental conditions on the selected outcomes. Mixed models are appropriate for correlated data (repeated measures) with various distributional assumptions and can easily accommodate missing data (31). A treatment-by-time interaction term was included in regression models to examine between condition differences in temporal patterns of MCA*v* across the day. Marginal means (i.e. adjusted mean of the dependent variable when fixed effects are held at their mean), were calculated for individual time points and within condition comparisons, relative to baseline, were performed for the sum of bilateral MCA*v*. Between condition comparisons of individual time points were performed on heart rate and mean arterial pressure variables. All models were adjusted for baseline, age, sex, waist circumference and treatment order. Models with MCA*v* as the dependent variable were additionally adjusted for mean arterial pressure (MAP), which was recorded simultaneously with MCA*v*. Due to the large number of comparisons in the within and between condition analysis of individual time points, adjustment for multiple comparisons using a Šidák correction was performed. A probability level of 0.05 was adopted. Statistical analyses were performed using Stata 15 for Windows (StataCorp LP).

RESULTS

Exercise response

The initial 30-minute exercise bout induced similar ($p>0.05$) heart rate and RPE responses (mean±SD) under each condition (EX+SIT: 104±10 bpm, 69±7% HRmax, 11±3 RPE; EX+BR: 108±15 bpm, 72±11 %HRmax, 11±3 RPE). Average HR and RPE across all 12 walking breaks was 93±14 bpm, 62±10%HRmax and 8±2 RPE.

Temporal variation: 8hr pattern of cerebral blood velocity

Recording the MCA*v* across an eight-hour time period enabled the assessment of the pattern of cerebral blood velocity across the day. Observation of the response across time revealed a persistent decline in SIT (Figure 2A). In the EX+SIT and EX+BR conditions, the initial decline of MCA*v* was followed by an afternoon recovery (Figure 2B, C). In support of these observations, a significant main effect of time was found for the sum of bilateral velocities ($p<0.001$). Post hoc analysis revealed a negative linear trend in SIT ($p<0.001$) but a positive quadratic trend for both EX+SIT ($p<0.001$) and EX+BR ($p <0.01$). A positive quadratic trend identifies the response as a convex curvilinear pattern. A significant main effect of time was also observed for left MCA*v* ($p<0.001$) and right MCA*v* ($p=0.04$). Left MCA*v* followed a negative linear trend in SIT ($p<0.001$) but a positive quadratic trend in EX+SIT ($p<0.001$) and EX+BR ($p <.001$). Right MCA*v* followed a negative linear trend for SIT ($p<0.001$), a positive quadratic trend in EX+SIT ($p=0.02$) and no significant trend for EX+BR ($p>0.05$). Within condition analysis of the time course data in the SIT condition revealed a significant decline in the sum of bilateral MCA*v* during the morning period relative to baseline, which was sustained until the end of the condition (Figure 2A). However, an initial decline in

MCA*v* relative to baseline was followed by a recovery, which was sustained for the final 2.5 hours of the EX+SIT condition, and final 4 hours of the EX+BR condition (Figure 2B, C).

Average cerebral blood velocity across the day

The sum of bilateral velocities (cm/s), averaged across the day (Figure 3A), was higher in the EX+SIT condition 87 [95% CI 79-96] relative to SIT 85 [76-93, p=0.005] or EX+BR 85 [77-93, p=0.02]. These between condition differences in MCA*v* (cm/s) were largely driven by the left MCA, which was higher in EX+SIT 44 [42-46] compared to SIT 43 [41-45, p=0.009] or EX+BR 42 [40-44, p<0.001] (Figure 3C). However, no significant differences were observed between conditions in the average right MCA*v* (cm/s); SIT 45 [40-51], EX+SIT 45 [40-50], and EX+BR 46 [41-51] (Figure 3B).

Comparison between conditions in hemodynamic data

Heart rate, when averaged across the day, displayed a pattern of increase with increasing activity; SIT 68 [64-71], EX+SIT 72 [69-75, p<0.001 vs. SIT], and EX+BR 73 [70-77, p<0.001 vs. SIT]. This was predominantly due to increased heart rate following the 30-minute bout of moderate-intensity exercise. In EX+SIT and EX+BR, heart rate remained elevated for approximately 2 hours following the moderate-intensity exercise bout, relative to SIT (Figure 4A). Despite a higher heart rate, mean arterial pressure was lower for approximately 2 hours following the moderate-intensity exercise bout in EX+SIT and EX+BR, relative to SIT, although no significant differences between conditions were observed during this time. There was a small increase in the mean arterial pressure (mm Hg) averaged across the day in EX+BR 102 [96-107], compared to SIT 98 [92-104, p=0.02], but no difference compared to EX+SIT 99 [93-105].

DISCUSSION

We observed that the pattern of MCA*v* during prolonged uninterrupted sitting was that of negative linear trend, with significant declines relative to baseline during the final 3.5 hours of the experiment. In contrast, the pattern of MCA*v* following a morning bout of exercise with or without breaks in sitting, was that of a convex curvilinear response characterized by an initial decline followed by a subsequent recovery. Interestingly, the recovery of MCA*v* after the initial decline began earlier in the EX+BR condition, compared to EX+SIT, which may represent a benefit of intermittent walking on the temporal pattern of MCA*v*. The clinical implications of such a pattern of MCA*v* may be in avoiding sharp declines in the delivery of oxygen and nutrients to the brain (34). A decline in the delivery of glucose to the brain for example, risks exposing the brain to hypoglycaemia which can increase the risk of developing dementia (41). Previously, we hypothesized that *fluctuations* in glucose availability, more specifically than *absolute* concentrations, pose a risk to brain health and breaks in sitting may help mitigate this risk by maintaining a more stable supply of glucose to the brain (40). While the current data suggest that MCA*v* was most stable in the EX+BR condition, we did not measure glucose availability to the brain. Future studies to determine the effect of breaks in sitting on central glucose concentrations and oxygen delivery would be highly informative. To our knowledge, this is the first study to examine the 8-hour pattern of MCA*v* in this way. This type of analysis involving frequent transcranial Doppler assessment offers unique insights into the temporal regulation of cerebral blood flow, and may have implications for understanding cerebrovascular health.

Insert figure 2 about here

We also observed that a morning bout of exercise sustained a higher average MCA*v* across a subsequent period of prolonged sitting. However, the finding that adding regular activity breaks to a morning bout of exercise abolished the increase in average MCA*v* was somewhat unexpected. There are some possible explanations worth exploring. 1) Day to day differences in the probe angle and location used when establishing the MCA*v* signal may have introduced measurement error into the between condition comparisons of average MCA*v*. Our within condition analysis of the pattern of MCA*v* helps mitigate this potential source of error as participants remained instrumented for the entire experiment to avoid relocating the MCA. 2) Subtle changes in MCA diameter, undetectable by TCD, may have altered MCA*v* during intermittent walking. Using magnetic resonance imaging, both increases and decreases in MCA diameter have been observed following hypercapnia and rhythmic handgrip exercise respectively (8, 38). While it is unknown what effect, if any, intermittent walking would have on MCA diameter, an increased diameter would translate to a decrease in velocity and vice versa for a decreased diameter, assuming constant flow.

Insert figure 3 about here

The effects of intermittent walking on MCA*v* have been documented in one previous study of lean healthy 'desk workers' (6). The authors demonstrated an increase in MCA*v* pre to post a 4 hour period involving breaks in sitting, compared to prolonged uninterrupted sitting (6). Although we observed an attenuation in average MCA*v* following intermittent walking, this was after an antecedent bout of morning exercise in a population of older overweight and obese adults (mean age 70 years), compared to walking breaks alone in a younger healthy population (mean age 36 years) in the study by Carter *et al.* These differences between

studies likely represented a different stimulus to a range of mechanisms responsible for regulating cerebral blood flow.

Whilst our study was not designed to address the mechanisms responsible for effects on MCA*v*, several possibilities may exist. Brain blood flow is controlled by multiple redundant and integrative mechanisms and is highly protected by local and reflex pathways. Although differences existed between conditions in blood pressure responses (Figure 4), MCA*v* data were statistically adjusted for contemporaneous blood pressure in regression analyses and it is therefore unlikely that our cerebrovascular findings are primarily related to underlying changes in driving pressures. This type of correction avoids the need to meet the stringent assumptions required for ratio normalisation, where one number is divided by another (9). A further mechanism that controls cerebral blood flow is the partial pressure of carbon dioxide in the circulating blood and it is possible that the exercise bouts induced differences in this parameter. However, the major differences we observed between conditions occurred more than 4 hours after the morning exercise bout and all of our MCA*v* data were obtained under quiet resting conditions. Furthermore, an impact of active breaks on carbon dioxide at the time of measurement seems unlikely, since there was ~25 minutes between these brief periods of walking and the subsequent resting measure of MCA*v*.

Insert figure 4 about here

A strength of this study is the well-controlled randomized crossover design which controls for person-specific factors and affords smaller sample sizes. Trial conditions were also standardized for potential confounders such as diet, physical activity, medications and

baseline values. There are also some limitations to our study. The experiment was designed as a superiority trial, and we did not include a fourth condition involving walking breaks alone. This was due to the general acceptance of the health benefits associated with continuous exercise bouts; we considered this the minimum standard for prescription. Our aim in the present study was to determine whether additive benefit was possible beyond that obtained from a morning bout of exercise. Our measure of cerebrovascular function, based on transcranial Doppler ultrasound, is widely used, provides sensitive time course information and has been shown to be a useful surrogate measure of cerebral blood flow between individuals (26). However, direct measures of intracranial diameters are not currently possible using ultrasound and velocity is therefore relied upon as a surrogate measure of flow. This is less of an issue for within subject experimental designs because blood flow changes are heavily dependent upon velocity change. However, we cannot rule out distinct effects on artery diameter responses that went undetected. Future experiments utilizing electroencephalography (EEG) or near-infrared spectroscopy (NIRS) may help to better understand complementary and temporal patterns of change in cerebrovascular function in the future. Further, positron emission tomography (PET) and magnetic resonance imaging (MRI) would provide information on spatial distribution of brain blood flow. In addition, it is unknown whether the changes observed simply represent a local effect on the brain vessels per se, or an impact on cerebral activation that subsequently affected brain blood vessels. Future studies, perhaps including fMRI may be utilized to test how brain networks are affected by the combination of exercise and breaks in sitting. This is relevant since metabolic activity in the brain is known to also affect regional cerebral blood flow. Finally, given expected regional differences in cerebral blood flow, our findings are not generalizable to the posterior circulation.

383 *Conclusion*

384 We have demonstrated in older overweight to obese adults, that the pattern of cerebral blood
385 velocity over eight hours is improved following a morning bout of moderate-intensity
386 exercise with or without subsequent breaks in sitting. In addition, a morning bout of exercise
387 sustained a higher average MCA*v* during a period of subsequent sitting. Interestingly, adding
388 intermittent walking breaks to a morning bout of exercise abolished the increase in average
389 MCA*v*, which was unexpected. Future studies should seek to replicate these findings with
390 more direct measures of cerebral blood flow using PET or MRI. In addition, future studies
391 using TCD should take advantage of the high temporal resolution this measure offers, and
392 collect frequent recordings to analyse the temporal *pattern* of cerebral blood velocity.
393 Collecting and analysing data in this way can also take advantage of current statistical
394 techniques such as linear mixed effects modelling, which are particularly suited to repeated
395 measures analysis and within subject study designs. In conclusion, our findings suggest that
396 uninterrupted sitting should be avoided, and moderate-intensity exercise should be
397 encouraged for the daily maintenance of cerebral blood flow.

GRANTS

This work was funded by a project grant from the National Health and Medical Research Council of Australia (1062338). M.J.W was supported by the University of Western Australia and the Baker Heart and Diabetes Institute. D.W.D was supported by a NHMRC Senior Research Fellowship (NHMRC APP1078360). I.H. was supported by the University of Turku, Hospital District of South-West Finland and the Juho Vainio Foundation. E. C. was supported by an ARC Future Fellowship (ARC FT140100085). P.N.A was supported by a Canadian Research Chair. D.J.G was supported a NHMRC Principal Research Fellowship (APP1080914).

DISCLOUSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

DJG, MJW, LN, KAE, EC and DWD were involved in the study design. PNA established the transcranial Doppler protocol. BS, KS, AS, JL, IH were involved in recruitment and data collection. MJW, BS and EC were involved in data analysis. DJG, MJW and DWD prepared the manuscript. All authors edited the manuscript and approved the final version.

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Figure legends

Figure 1. Experimental design. Participants completed three conditions in a random order separated by a minimum of six days. Conditions are as follows Sitting (SIT): uninterrupted sitting (8hr, control); Exercise + Sitting (EX+SIT): sitting (1hr), moderate-intensity walking (30min, denoted by walking figure) followed by uninterrupted sitting (6.5hr); Exercise + Breaks (EX+BR): sitting (1hr), moderate-intensity walking (30min) followed by sitting (6.5hr) interrupted every 30 minutes with 3 minutes of light-intensity walking. Walking breaks are denoted by vertical lines in the EX+BR condition. During each condition, participants consumed a standardized breakfast and lunch meal and transcranial Doppler, mean arterial pressure and heart rate were recorded simultaneously across the day.

Figure 2. The sum of bilateral velocities across the day. Panels A, B and C represent the velocity trace displayed as a change from baseline during the SIT, EX+SIT and EX+BR conditions, respectively. Baseline values (cm/s) in each condition are; SIT 96 [90-101]; EX+SIT 95 [89-101]; and EX+BR 93 [87-99]. Dotted lines represent the timing of the standardized meals and the shaded area denotes the timing of the moderate-intensity exercise bout. Data are marginal mean + 95% CI, adjusted for baseline, age, sex, waist circumference, treatment order and mean arterial pressure. *$p<0.05$ within condition relative to baseline.

Figure 3. Between condition comparison of cerebral blood velocity. Panels A, B and C represent the sum of bilateral velocities, left MCA*v* and right MCA*v* respectively, displayed as an average across the day. Data are marginal means + 95% CI, adjusted for baseline, age, sex, waist circumference, treatment order and mean arterial pressure. MCA*v*, middle cerebral artery velocity.

Figure 4. Between condition comparison of heart rate and mean arterial pressure. Panels A and C represent heart rate and mean arterial pressure respectively, displayed as a time course across the day. Panels B and D represent the heart rate and mean arterial pressure respectively, displayed as an average across the day. Dotted lines represent the timing of the standardized meals and the shaded area denotes the timing of the moderate-intensity exercise bout. Data are marginal means ± 95% CI, adjusted for baseline, age, sex, waist circumference and treatment order. *$p<0.05$ relative to SIT. MAP, mean arterial pressure.

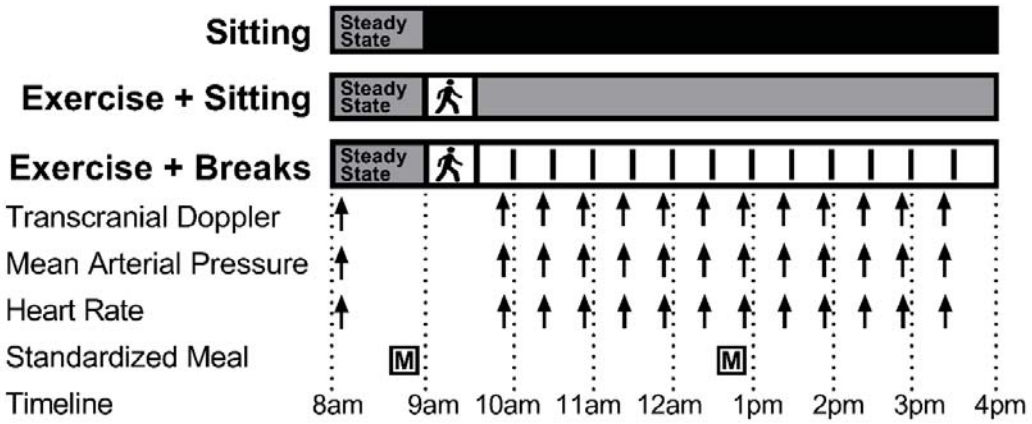

Figure 1.

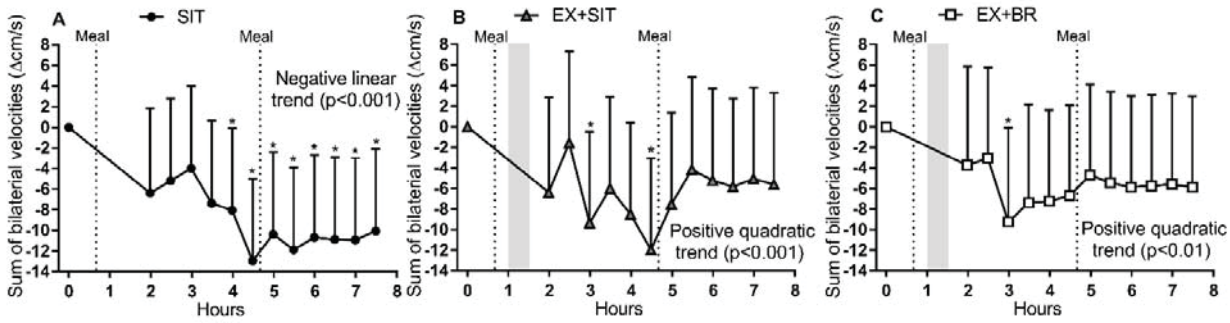

Figure 2.

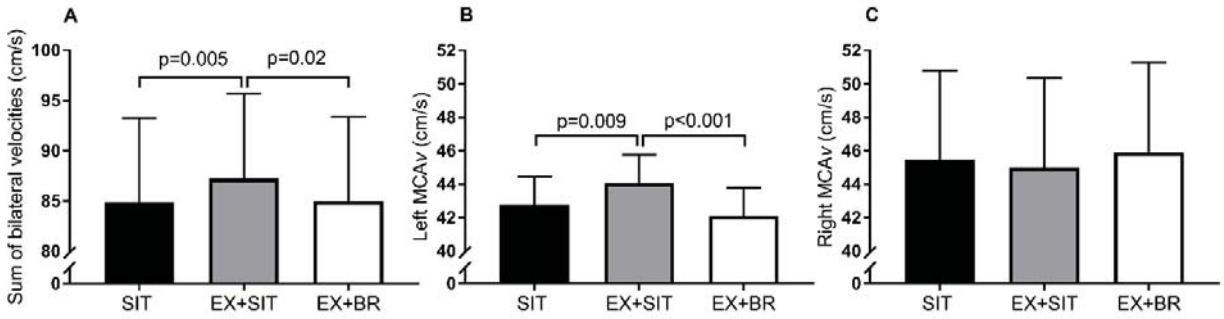

Figure 3.

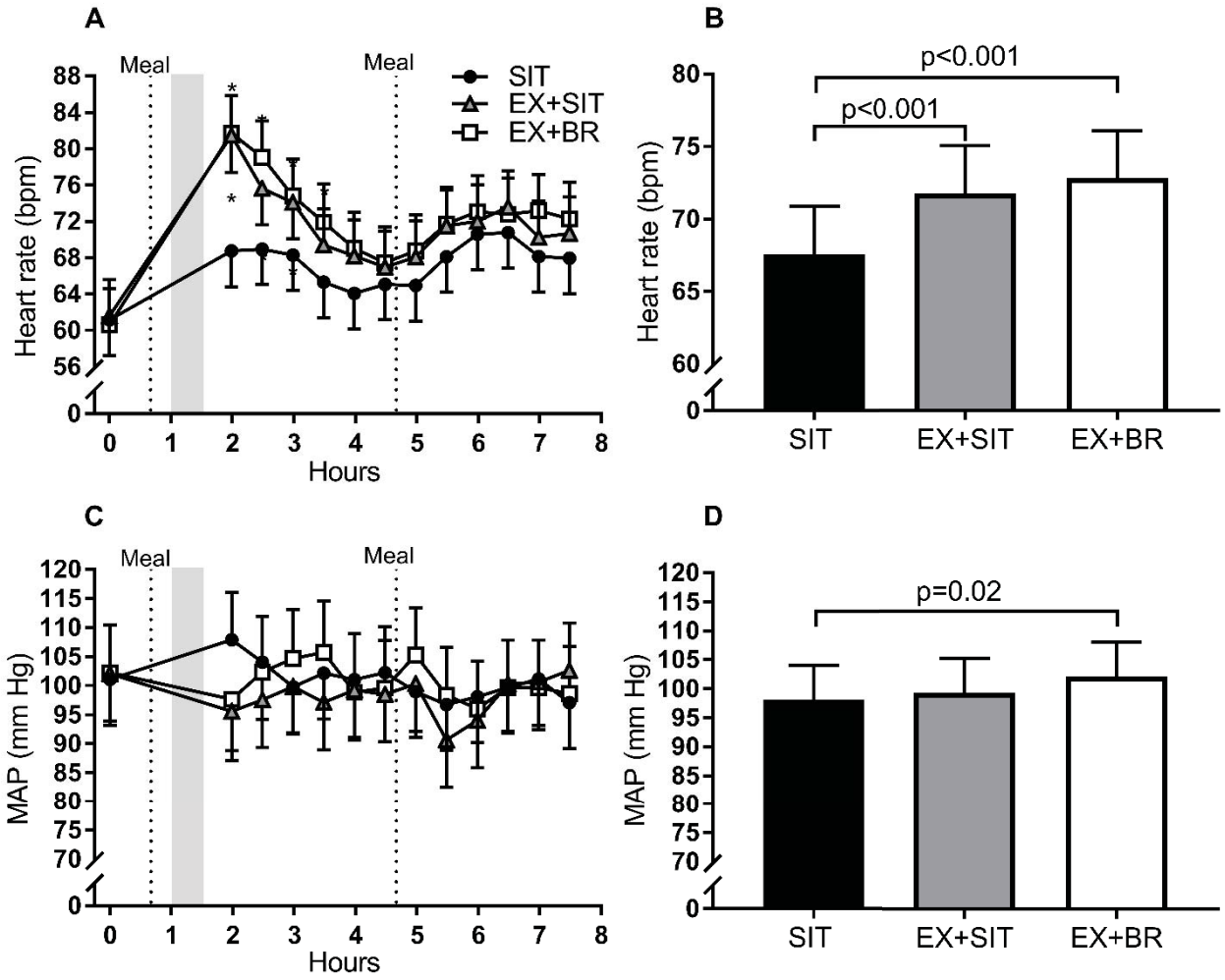

Figure 4.

Tables

Table 1. Participant characteristics.

Demographic	Baseline
N	12
Sex (female/male)	2 / 10
Age (years)	70±7
Body mass index (kg/m^2)	30.4±4.3
Waist circumference (cm)	103.4±11.0
Office SBP (mmHg)*	128±13
Office DBP (mmHg)*	76±13
Fasting glucose (mmol/L)†	5.0±0.5
Fasting insulin (pmol/L)†	30±24.7
Fasting cholesterol (mmol/L)†	5.1±0.9
Fasting triglycerides (mmol/L)†	1.1±0.4
Fasting HDL (mmol/L)†	1.3±0.3
Fasting LDL (mmol/L)†	3.3±0.6

Data are mean±SD; SBP, systolic blood pressure; DBP, diastolic blood pressure HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; *measured during familiarisation visit, †measured during first experimental visit