RESEARCH ARTICLE

Simple intermittent resistance activity mitigates the detrimental effect of prolonged unbroken sitting on arterial function in overweight and obese adults

Rachel E. Climie,1,2* Michael J. Wheeler,1,3* Megan Grace,1 Elisabeth A. Lambert,1,4 Neale Cohen,1 Neville Owen,1,4 Bronwyn A. Kingwell,1,5 David W. Dunstan,1,3,6,7,8,9 and Daniel J. Green3

1Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia; 2Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia; 3School of Human Sciences (Exercise and Sport Science), The University of Western Australia, Perth, Western Australia, Australia; 4Swinburne University of Technology, Melbourne, Victoria, Australia; 5Central Clinical School and Department of Physiology, School of Medicine, Nursing and Health Services, Monash University, Melbourne, Victoria, Australia; 6School of Public Health, University of Queensland, Brisbane, Queensland, Australia; 7Mary MacKillop Institute of Health Research, Australian Catholic University, Melbourne, Victoria, Australia; 8School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia; and 9School of Exercise and Nutrition Sciences, Deakin University, Burwood, Victoria, Australia

Submitted 18 June 2018; accepted in final form 5 September 2018

Climie RE, Wheeler MJ, Grace M, Lambert EA, Cohen N, Owen N, Kingwell BA, Dunstan DW, Green DJ. Simple intermittent resistance activity mitigates the detrimental effect of prolonged unbroken sitting on arterial function in overweight and obese adults. J Appl Physiol 125: 1787–1794, 2018. First published September 6, 2018; doi:10.1152/japplphysiol.00544.2018.—Prolonged sitting contributes to cardiovascular disease (CVD) risk. The underlying mechanisms are unknown but may include changes in arterial function and vasoactive mediators. We examined the effects of prolonged unbroken sitting, relative to regular active interruptions to sitting time, on arterial function in adults at increased CVD risk. In a randomized crossover trial, 19 sedentary overweight/obese adults (mean ± SD age 57 ± 12 yr) completed 2 laboratory-based conditions: 5 h uninterrupted sitting (SIT) and 5 h sitting interrupted every 30 min by 3 min of simple resistance activities (SRA). Femoral artery function [flow-mediated dilation (FMD)], blood flow, and shear rate were measured at 0 h, 30 min, 1 h, 2 h, and 5 h. Brachial FMD was assessed at 0 and 5 h. Plasma was collected hourly for measurement of endothelin-1 (ET-1), nitrates/nitrites, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). There was a significant decline in femoral artery FMD, averaged over 5 h in the SIT condition, relative to SRA (P < 0.001). Plasma ET-1 total area under the curve over 5 h increased in the SIT condition compared with SRA (P = 0.006). There was no significant difference between conditions in femoral or brachial shear rate, brachial FMD, nitrates/nitrites, VCAM-1, or ICAM-1 (P > 0.05 for all). Five hours of prolonged sitting, relative to regular interruptions to sitting time, impaired femoral artery vasodilator function and increased circulating ET-1 in overweight/obese adults. There is the need to build on this evidence beyond acute observations to better understand the potential longer-term vascular-related consequences of prolonged sitting.

INTRODUCTION

Arterial dysfunction, particularly that related to the inner (endothelial) lining, represents one of the earliest detectable stages of atherosclerotic disease (2, 24). Atherosclerotic lesions are not uniformly distributed, developing primarily in the coronary and carotid arteries as well as in the lower limb (21), which suggests that local factors, such as abnormal arterial shear stress, may play a role. Shear stress is modulated by physical (in)activity and sedentary behaviors (i.e., prolonged sitting (25, 32, 38, 39)), making such activities key contributors to arterial (dys)function and atherosclerosis. Excessive time spent sitting is now ubiquitous in modern-day society, with the average adult spending 9 h a day sitting (17). Moreover, prolonged sitting (defined as >30 min of uninterrupted sitting) accounts for 4 h per day (3). Importantly, high volumes of sitting are associated with elevated risk of cardiovascular disease (CVD) (31) along with other adverse health consequences (5), and it is possible that sitting-induced decrements in arterial function contribute to increased risk of CVD.

Previous research has shown that prolonged sitting leads to impairment in lower limb arterial function and dilation, effects that may be negated or reversed by light-intensity activity (25, 32, 38). These studies have been restricted to young, healthy populations, and it is unknown whether prolonged sitting may affect arterial function in those already at a heightened risk of CVD (such as overweight/obese adults). Moreover, mechanisms relating to the effect of prolonged sitting on vascular function remain unexplored. Candidate mechanisms include nitric oxide (NO), a potent vasodilator released from endothelial cells in response to shear stress (10). Furthermore, high insulin concentration (such as in insulin-resistant type 2 diabetes or overweight/obese populations) is associated with en-
dothelin-1 (ET-1; a vasoconstrictor) upregulation (6, 29, 33) and expression of pro-atherogenic molecules [intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)] (26). It is conceivable that the combination of CVD risk factors and reduced shear stress in the lower limb associated with prolonged sitting promotes an exaggerated pro-atherogenic environment. However, this hypothesis has not been directly addressed in those at increased risk of CVD.

Most earlier work has examined the effect of interrupting prolonged sitting with intermittent walking activity, but it has been suggested that a more pragmatic option for working adults could be to interrupt sitting without having to move away from their workstation, for example by performing simple resistance activities (SRA) in a static position using their own body weight (11). Indeed, a recent study in patients with type 2 diabetes demonstrated that interrupting prolonged sitting with brief bouts of SRA was as effective as light walking for reducing the impact of a day of uninterrupted sitting on postprandial glucose and insulin (11). However, it is unclear whether benefits in arterial function could be gained via SRA during periods of prolonged sitting. The aim of this study was to examine the effects on arterial function of prolonged uninterrupted sitting, relative to regular physically-active interruptions (SRAs) to sitting time, in adults at increased CVD risk.

MATERIALS AND METHODS

Subjects

Sedentary overweight/obese [body mass index (BMI) ≥25–40 kg/m²] adults were recruited via local advertisements. The exclusion criteria included pregnancy, self-reported sitting less than 5 h per day, self-reported regular engagement in moderate- to vigorous-intensity physical activity (≥150 min/wk), diagnosed diabetes, use of glucose/lipid lowering medications, being a current smoker, or having any major acute or chronic illness that might limit their ability to perform the SRA. Premenopausal women were excluded, as assessed via self-report. One woman who reported being perimenopausal completed both study conditions; sensitivity analysis (data not shown) revealed that statistical significance and interpretation of the experiment were unaltered by inclusion/exclusion of this participant’s data.

Study Overview and Randomization

This study was a randomized crossover trial (ACTRN12-316000578404), undertaken at the Baker Heart and Diabetes Institute research clinic. Potential participants were initially screened via a telephone questionnaire to determine their eligibility and were asked about their general health and medical history. Eligible participants were requested to undergo a fasted screening blood test at a local pathology clinic (Melbourne Pathology; Sonic Healthcare Ltd.) for glycated hemoglobin, glucose, and lipid profile. Participants attended the laboratory on three separate occasions: a familiarization visit and two trial visits (Fig. 1). Trial condition order was randomized by a third party (block-randomization and balanced block sizes) and stratified by sex. Study personnel were blinded to the condition order until familiarization, and participants were blinded to the condition order until their first condition visit. Sample analyses (including arterial function analysis) were performed by trained personnel who were blinded to the condition order. The trial was approved by the Alfred Human Ethics Committee and was performed in accordance with the Declaration of Helsinki, and all participants provided signed informed consent.

Fig. 1. Study design and protocol. Participants were initially screened over the phone, followed by a screening blood test if eligible. Eligible participants then attended the laboratory on three occasions: familiarization followed by two experimental conditions in a random order. FMD, flow mediated dilation; SIT, uninterrupted sitting condition; SRA, sitting interrupted by simple resistance activities condition.

Study Protocol

Participants attended a familiarization session 1 wk before their first condition visit, at which they were shown the testing procedures and measurements. Height, weight, and waist and hip circumference were obtained in duplicate via standard methods. To minimize any diet-induced variability, participants consumed a standardized meal the evening prior and on the day of the experimental condition. Each meal was standardized to meet 33% of each participant’s daily energy requirements, estimated using the Schofield equation (34). Using FoodWorks Software (FoodWorks Xryris, 2012), all meals were matched for macronutrients of 12%–15% energy from proteins, 53%–55% energy from carbohydrate, and 30%–33% energy from fat. Participants were instructed to consume their standardized meal the evening before each condition between 1900 and 2100 and to fast until the next morning. Participants were also instructed not to alter their habitual daily activities while involved in the study but to avoid moderate-to-vigorous exercise, caffeine, and alcohol for 48 h before each condition (restrictive phase referred to in Fig. 1) (33). This was confirmed upon presentation to the respective experimental condition days.

Experimental Conditions

On the trial days, participants arrived at the laboratory between 0730 and 0800 in a fasted state (>10 h). Weight was remeasured, and BMI was calculated. An indwelling venous catheter was inserted in the antecubital vein for blood sampling. Each condition began with a 1-h “steady-state” seated period. During the steady-state period, blood samples were collected, blood pressure (BP) was measured, femoral and brachial artery flow-mediated dilation (FMD) were recorded, and participants were then given 15 min to consume a standardized breakfast meal before the 0 h time point. Postprandial blood samples were collected at 30 min, 1 h, and then hourly up to the end of the 5-h condition. Options for the breakfast meal consisted of bran-based cereal, fruit salad, ham-and-cheese croissant, and juice (200 ml). Lunch was provided after 5 h (at the end of the condition and after the final FMD measurement) and options included a salad and meat bread roll and juice. A note was made regarding each individual’s meal choice, and these were replicated on the repeat attendance. Timing of medication (if applicable) was standardized to occur with the breakfast meal during each condition.

Participants were instructed to sit upright in a comfortable lounge chair for the duration of the condition and were asked to minimize
excessive movement. In the SIT condition, participants sat uninterrupted for 5 h, only rising from the chair to void. The SRA condition was similar, but sitting was interrupted every 30 min for 3 min of SRA. The SRA were light-intensity, body weight-resisted exercises undertaken in a standing posture, including half squats, calf raises, and single knee raises with gluteal contractions. These lower-body activities were selected because they are considered to be safe for most individuals; can be implemented easily using one’s own body weight without having to move away from the desk (unlike moving to a wall to perform wall pushups for the upper body, for example); involve large muscle groups (gluteal and quadriceps), thereby maximizing the effect of muscle-mediated glucose uptake and reducing postprandial glucose concentrations; and reduce the likelihood of dislodging the cannula (which may occur during upper body exercise). Each exercise was performed for 20 s at a tempo of 1 repetition every 2 s, 3 times, for a total of 3 min. To ensure appropriate movement standardization, tempo, and correct form, participants mimicked a video recording. Half squats and knee raises were tailored to the range of motion of each participant, where knee/hip angle was between 45° and 90° for half squats/knee raises, assessed during the familiarization session. The alternate trial condition was completed after a minimum of 6 days washout period.

**Measurements**

**Arterial function.** Participants were seated for 20 min in a dimly lit, temperature-controlled room (22°C –24°C) before the steady-state recording of FMD. Brachial and superficial femoral artery function (i.e., FMD) were assessed in the seated position using a high-resolution ultrasound machine (Terason t3200, Teratech, Burlington, MA) in conjunction with a 10 MHz multifrequency linear array probe and insonation angle of 60° according to current guidelines (36). Femoral artery FMD was measured in the right leg with the foot placed flat on the floor. A rapid inflatable cuff (SC-12-D, D.E. Hokanson Inc., Bellevue, WA) was placed around the thigh at the distal end of the femur. Once an optimal image of the artery was obtained, a 1-min recording of continuous resting vessel diameter and blood velocity was measured (live duplex mode). Resting shear rate was calculated as $4 \times \text{velocity in cm per second/diameter in cm}$, using the average velocity and diameter during the 1-min recording before cuff inflation. The cuff was then inflated for 5 min (200 mmHg). After 5 min of inflation, the cuff was released to induce reactive hyperemia. A further 3 min of continuous duplex ultrasound recording was then undertaken to observe the post-deflation diameter profile and peak response. The FMD response is presented as the percentage change from preceding resting diameter to peak dilation. Femoral artery FMD was measured at the start of the condition during the steady-state period (0 h), 30 min, 1 h, 2 h, and 5 h. Brachial FMD, resting blood flow, and resting shear rate were measured before the femoral measurements at the start of each condition and again at 5 h. The arm was extended and supported by a pillow at the level of the heart. The inflatable cuff was placed around the forearm, distal to the cubital fossa, and the artery was imaged following a similar protocol as that described for the femoral FMD measurement. FMD measurements were taken in the same limbs for all trial conditions. Impor-

![Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) diagram.](https://www.jappl.org)
tantly, all FMD measures occurred before the SRA to avoid measuring any transient effects of the SRA that might have influenced the measurement. We have previously published a reproducibility study utilizing the software and analytical approaches adopted in this experiment (42). Our coefficient of variation for intra-observer reproducibility when repeated analysis was undertaken on the same images by a single scanner was 6.7%. Between-visit reproducibility, when repeat scans were collected from the same operator and analyzed in a blinded manner, was 14.7% (this includes day-to-day biological variability).

Analyses of artery diameter and blood velocity were performed offline using automated edge detection and wall tracking software (42) by one scanner, who was blinded to the condition. Resting diameter and peak diameter post cuff release was used to calculate FMD percentage change. Shear rate (s⁻¹), calculated from blood velocity and diameter, was used as an estimate of shear stress on the artery wall. The shear stimulus was calculated as the shear rate area under the curve (AUC) from time of cuff release to peak dilatation, using the sum of trapezoids method.

Resting BP. Hourly resting brachial BP was measured in triplicate at 1 min intervals, using an automated oscillometric BP monitor (Dinamap Vital Signs Monitor 18446SX, HEM-907, Omron, Kyoto, Japan) and an appropriately sized cuff, as per recommended guidelines (8). All measurements were taken in the same arm for both conditions by trained research staff. The first measurement was discarded, and the average of the second two was used in the analysis.

Biochemical analysis. Whole blood was collected into EDTA tubes and centrifuged within 5 min of collection (2,000 revolutions/min for 15 min at 4°C), and the plasma fraction was separated and stored at −80°C. Samples for ET-1, VCAM-1, and ICAM-1 were analyzed by sandwich immunoassay technique using kits from R&D systems (Minneapolis, MN) according to the manufacturer’s instructions. The final product of the ELISA was quantified using a Benchmark Plus Microplate spectrophotometer and standard curve (Bio-Rad Laboratories, Hercules, CA) at 450 nm (14). Plasma nitrate and nitrite were measured as an indirect measurement of total NO using a commercial colorimetric kit from Cayman Chemical Company (Ann Arbor, MI).

Statistical Analysis

The total AUC across the 5-h protocol on each day was calculated for ET-1, nitrates plus nitrates, ICAM-1, and VCAM-1 using the trapezoidal method. We examined within- and between-condition effects using generalized linear mixed models with random intercepts in Stata 14.2 (StataCorp LP). Outcome variables were adjusted for potential covariates to reduce the total variance of the model. All models were adjusted for age, sex, BMI, values at 0 h, and condition order. A condition by time interaction with post hoc comparisons was used to compare individual time points between conditions and within condition relative to 0 h. Post hoc comparisons between time points were adjusted for multiple comparisons using a Šidák correction. Associations between variables were assessed using Spearman’s rank correlation coefficients. Descriptive data are presented as means ± standard deviation (SD), and output from mixed model analyses are presented as marginal means ± standard error where \( P < 0.05 \) was considered statistically significant.

RESULTS

Participant Characteristics

Of the 21 participants randomized, 19 completed the study (Fig. 2). The mean ± SD age was 57 ± 12 yr, participants were all overweight or obese (30.6 ± 3.4 kg/m²), and 6 were taking medication for hypertension. The participant characteristics are presented in Table 1.

<table>
<thead>
<tr>
<th>Sex, male/female</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11/8</td>
</tr>
</tbody>
</table>

| Age, yr          | 57 ± 12 |
| Body mass index, kg/m² | 30.6 ± 3.4 |
| Waist circumference, cm  | 104.3 ± 10.3 |
| Clinic systolic blood pressure, mmHg | 121 ± 11 |
| Clinic diastolic blood pressure, mmHg | 74 ± 10 |
| Glycated haemoglobin, %  | 5.4 ± 0.4 |
| Glycated haemoglobin, mmol/mol | 35.5 ± 4.4 |
| Fasting glucose, mmol/l | 5.2 ± 0.8 |
| Fasting insulin, mmol/l | 110 ± 57 |
| HOMA2-IR   | 2.0 ± 1.0 |
| Fasting cholesterol, mmol/l | 5.4 ± 1.2 |
| Fasting triglycerides, mmol/l | 1.5 ± 0.6 |
| Fasting HDL cholesterol, mmol/l | 1.7 ± 0.4 |
| Fasting LDL cholesterol, mmol/l | 3.1 ± 0.9 |
| Angiotensin II receptor blockers, n (%) | 3 (16) |
| Angiotensin converting enzyme inhibitors, n (%) | 1 (5) |
| Calcium channel blockers, n (%) | 2 (11) |
| Diuretic, n (%) | 1 (5) |
| Serotonin reuptake inhibitors, n (%) | 2 (11) |

Data are mean ± SD unless otherwise stated. HDL, high-density lipoprotein cholesterol; HOMA2-IR, homeostatic model assessment index of insulin resistance; LDL, low-density lipoprotein cholesterol.

FMD and Hemodynamics

The hemodynamic and absolute (i.e., unadjusted) FMD data are presented in Table 2. Table 3 displays adjusted data with statistical comparisons. Femoral artery FMD was not significantly different at the 0 h time point between conditions, nor at the 30 min time point, but was significantly lower at 1 and 2 h in the SIT condition compared with SRA (3.3 ± 0.6% vs. 9.3 ± 0.6%, \( P < 0.001 \) and 5.4 ± 0.8% vs. 8.9 ± 0.8%, \( P = 0.007 \) respectively; Table 3, Fig. 3). Femoral artery FMD at 5 h was not significantly different between conditions (\( P > 0.05 \)). However, femoral artery FMD averaged across the 5-h day was lower in the SIT condition compared with the SRA condition (5.3 ± 0.6% vs. 8.4 ± 0.5%, respectively, \( P < 0.001 \); Fig. 3B). No significant differences between conditions were observed for brachial artery FMD at either the 0 or 5 h time point (\( P \) for both > 0.05). Additional adjustment for resting diameter or shear stimulus had no significant impact on the models for femoral or brachial FMD (\( P > 0.05 \)) and so were not included as covariates.

Mean resting femoral shear rate averaged across 5 h was lower in the SIT condition relative to SRA, although the difference did not reach statistical significance (23.1 ± 9.7/s vs. 45.7 ± 9.6/s, \( P = 0.052 \)). Mean resting femoral blood flow averaged across 5 h was lower in the SIT condition relative to SRA (1.6 ± 0.4 ml/s vs. 2.3 ± 0.4 ml/s, \( P = 0.049 \)). No differences in resting systolic or diastolic BP averaged across 5 h were observed between the SIT condition and SRA conditions (117 ± 2 mmHg vs. 115 ± 2 mmHg, \( P = 0.618 \) and 69 ± 1 mmHg vs. 71 ± 1 mmHg, \( P = 0.094 \), respectively). Mean heart rate averaged over 5 h was significantly lower in the SIT relative to SRA condition (70 ± 2 beats/min vs. 72 ± 2 beats/min, \( P = 0.003 \)).

Blood Biomarkers

Plasma ET-1 total AUC was 14% higher in the SIT condition relative to SRA (8.1 ± 0.3 pg-hr.ml⁻¹ vs. 7.0 ± 0.3 pg-hr.ml⁻¹, Fig. 3C).
Hemodynamics and absolute (i.e., unadjusted) flow-mediated dilation data during 5 h of uninterrupted sitting and sitting interrupted with simple resistance activities

<table>
<thead>
<tr>
<th></th>
<th>Femoral</th>
<th>Brachial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 h</td>
<td>30 min</td>
</tr>
<tr>
<td>SIT resting blood flow, ml/min</td>
<td>60 ± 8</td>
<td>118 ± 40</td>
</tr>
<tr>
<td>SRA resting blood flow, ml/min</td>
<td>60 ± 8</td>
<td>43 ± 43</td>
</tr>
<tr>
<td>SIT resting shear rate, s⁻¹</td>
<td>15.3 ± 2.6</td>
<td>29.7 ± 11.8</td>
</tr>
<tr>
<td>SRA resting shear rate, s⁻¹</td>
<td>17.2 ± 2.6</td>
<td>21.4 ± 12.2</td>
</tr>
<tr>
<td>SIT resting diameter, mm</td>
<td>7.0 ± 0.02</td>
<td>7.1 ± 0.02</td>
</tr>
<tr>
<td>SRA resting diameter, mm</td>
<td>6.9 ± 0.02</td>
<td>7.0 ± 0.02</td>
</tr>
<tr>
<td>SIT FMD, %</td>
<td>7.4 ± 0.7</td>
<td>6.3 ± 0.9</td>
</tr>
<tr>
<td>SRA FMD, %</td>
<td>6.2 ± 0.7</td>
<td>6.4 ± 0.9</td>
</tr>
</tbody>
</table>

Data are mean ± SD. au, arbitrary units; AUC, total area under the curve; FMD, flow-mediated dilation; SIT, uninterrupted sitting; SR, shear rate; SRA, sitting interrupted with simple resistance activities. **P ≤ 0.01 between conditions, ***P ≤ 0.001 between conditions, †P < 0.05 within condition vs. 0 h.

DISCUSSION

The principal novel finding of this study was that femoral artery function (measured via FMD) was lower in the SIT condition relative to SRA at the 1 and 2 h time points, suggesting that introducing intermittent activity breaks during the first 2 h of prolonged sitting appears to exert the greatest impact on lower limb arterial function. We also found that ET-1 was significantly elevated following 1 h of prolonged sitting, compared with the SRA condition. These findings provide pathophysiologic insights into the impact of prolonged uninterrupted sitting on arterial dysfunction and increased CVD risk in overweight/obese adults.

We measured femoral artery FMD at multiple time points across 5 h. The magnitude of the decline in femoral FMD in the SIT condition was greatest after 1 h of uninterrupted sitting. In line with previous work (38, 39), this suggests that the first hour of prolonged sitting could elicit the greatest impact on femoral artery function and corresponds with the immediate diminishing of leg blood flow upon sitting (41). In addition, the relative insulin resistance induced by prolonged sitting after a meal (compared with sitting interrupted by breaks) (9, 13), may be associated with impaired arterial function and blood flow via effects on NO bioavailability and ET-1 (19, 20). It should be noted, however, that our subjects acted as their own controls in this crossover designed study, and they consumed exactly the same standardized breakfast and lunch meal for each condition, as well as evening meal the night before the trial day. Our study was well controlled in this regard, relative to many previous experiments.

We observed a slight rebound effect in femoral FMD at 5 h. However, differences between the SIT and SRA conditions did persist to some extent, even at the 5 h time point (2.6% FMD difference between conditions). There are a number of reasons that may explain this rebound effect, including a gradual cooling of muscle tissues.
diminution in terms of shear rate and/or habituation in terms of other mechanisms (oxidative or inflammatory effects). Since we did not assess glyceryl trinitrate (GTN) responses, the possibility also remains that a form of tachyphylaxis may occur in smooth muscle cells to repeated NO exposure.

The reasons for a sitting-induced decline in FMD are not completely understood but may be due to reductions in shear stress and blood flow (41, 42) as well as an increase in blood viscosity (16) in the SIT condition. Although we observed a marked decrease in femoral artery FMD in the SIT condition, we did not observe a concomitant decrease in resting shear rate or blood flow, as observed in some previous studies (14, 32, 38). The participants in these earlier studies were, however, young healthy adults, which is in contrast to the relatively older, overweight to obese, and sedentary population included in the current analysis. It is possible that shear and function relationships differ with age and long-term exposure to CVD risk factors (35).

Femoral FMD was elevated at 1 h and 2 h in the SRA condition relative to the SIT condition. This is similar to previous work in healthy populations, which has demonstrated that interrupting sitting with light-intensity walking (32, 38), moderate-intensity activity breaks (25), or “fidgeting” (27) improves lower limb artery function relative to prolonged uninterrupted sitting. The increase in femoral FMD observed in the current study occurred despite no within-condition increase in resting blood flow or shear rate, which has been reported in previous work (27, 32, 38). This suggests that the improvement in FMD seen with the introduction of intermittent SRA could be due to intrinsic improvement in vessel wall function and not merely an increase in the FMD stimulus. It is pertinent to mention that the FMD measurement occurred before the SRA break in our study, as opposed to immediately following exercise, as in some previous experiments (7, 32). We therefore avoided any transient impact of activity-related blood flow and shear rate changes on FMD. McManus et al. (25) also measured shear rate and FMD before activity breaks and observed no difference in shear rate compared with the sedentary condition. Despite no between-condition differences in resting blood flow at individual time points, we did observe a between-condition difference in the resting blood flow averaged over 5 h. Therefore, we cannot completely rule out the possibility that differences in blood flow and arterial hemodynamics may, in part, explain the differences observed in FMD.

Relative to SRA, ET-1 AUC was elevated across the 5 h of the SIT condition. ET-1 is a potent vasoconstrictor that plays a role in regulating vascular tone and blood flow, especially in older populations (37, 40). There was a weak but significant correlation between ET-1 and resting blood flow and similarly between ET-1 and resting shear rate. Indeed, it has been demonstrated that low levels of shear stress stimulate ET-1 secretion from cultured cells, whereas higher levels of shear stress have an inhibitory effect (22). In addition, sustained increases in shear stress following hand heating have been shown to result in uptake and clearance of arterial ET-1 via endothelin type B (ETB) receptors (4). The authors of this study noted that by blocking the ETB during hand heating, the decline in arterial ET-1 was prevented and radial artery FMD was reduced, despite sustained increases in shear stress. It is possible that the weak correlation between shear rate and ET-1 and lack of correlation between ET-1 and FMD in the current study may be due to measuring venous rather than arterial concentrations of ET-1. That said, our observation of elevated ET-1 in the SIT condition suggests that in older, sedentary, and at-risk populations, interactions between blood flow, shear stress, and ET-1 may contribute to sitting-induced impairment in arterial function. More work is required to confirm our findings.
In keeping with previous studies (32, 39), we did not observe a significant reduction in brachial FMD in the SRA condition compared with SIT. It should be noted, however, that brachial FMD was only measured at the start and end of each condition, and the possibility remains that transient differences may have occurred throughout the day. This is supported by the time course of effect in the femoral artery FMD, where differences were less apparent at 5 h than they were throughout the intervention period. Furthermore, it is also likely that the SRA had a varied effect on the upper and lower limbs. Alternatively, sitting may differentially impact upper and lower limb artery function, given that in the seated position, the lower limbs are subjected to unique structural and functional milieu (39). Upper body SRA may have been a better stimulus for improvements in brachial FMD; however, given that atherosclerotic lesions develop primarily in the lower limbs (1, 21), the primary focus of this work was the effects of SIT versus SRA on the lower body. Future studies utilizing similar measurement time points for both the brachial and femoral arteries will be necessary to establish or definitively rule out a generalized arterial effect of prolonged sitting (18, 28, 30).

Although we did not observe differences in BP between conditions, an increase in average heart rate across 5 h was evident in the SRA condition relative to SIT. The absence of a BP-lowering impact of activity breaks contrasts with previous evidence demonstrating that regular walking breaks or SRA can lower BP relative to prolonged sitting (12, 23). It should be noted that the resting BP of our study population was relatively low and possibly indicates limited potential for improvement.

Limitations

This study was performed in a laboratory setting, and although this environment allows for rigorously controlled trials to be conducted, it does not reveal the impact of prolonged sitting on arterial function in a real-life setting, such as in the workplace or at home. Moreover, we did not assess changes in GTN responses, which limits our findings to changes in arterial function or NO-mediated dilator function, rather than specifically to endothelial function. We adopted a seated “steady-state” period, rather than supine, which may have influenced our data, given the impacts of seated postures on blood flow (32, 41). However, we undertook a resting baseline period in accordance with current guidelines regarding optimal FMD and BP assessment (36) and utilized a seated posture during this phase so as to be consistent with subsequent seated postures throughout the experiment; a change in posture from supine to seated may have equally influenced our data. We only measured brachial FMD at 0 and 5 h, limiting the possibility to examine any transient effects in upper limb FMD across the day. Furthermore, only lower body SRAs were performed. Future work may examine whether similar activities in the upper limb have the same effect on arterial function. Finally, our results cannot be generalized beyond the current study population, and further research is needed to compare the effect of prolonged sitting, compared with breaks in sitting, on arterial function in other high risk groups.

Conclusion

This is the first study to show that prolonged, uninterrupted sitting has detrimental effects on arterial function in older, overweight/obese adults at heightened risk of CVD across a 5-h day. We also demonstrate that brief periods of simple resistance exercise effectively mitigates this impairment. Given the ubiquitous high volumes of prolonged sitting in contemporary work and recreational settings, and the associated increased risk of CVD and all-cause mortality (5, 15), short, frequent bouts of light-intensity resistance activities may provide a practical and easily translated approach to maintaining healthy arterial function, particularly within the first 2 h of prolonged sitting. Future work should aim to examine the longer-term impacts of prolonged unbroken sitting, and the impacts of different interventions that interrupt this ubiquitous behavior, on arterial (dys)function in high risk populations.

REFERENCES


