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Interrupting Prolonged Sitting with Brief Bouts of Light Walking or Simple Resistance Activities Reduces Resting Blood Pressure and Plasma Noradrenaline in Type 2 Diabetes

Short title: Interrupting Sitting and Blood Pressure

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ABSTRACT

Objective: Prolonged sitting is increasingly recognized as a ubiquitous cardiometabolic risk factor, possibly distinct from lack of physical exercise. We examined whether interrupting prolonged sitting with brief bouts of light-intensity activity reduced blood pressure (BP) and plasma noradrenaline in type 2 diabetes (T2D).

Methods: In a randomized crossover trial, 24 inactive overweight/obese adults with T2D (14 men; mean±SD; 62±6 y) consumed standardized meals during 3 x 8 h conditions: uninterrupted sitting (SIT); sitting + half-hourly bouts of walking (3.2 $km \cdot h^{-1}$ for 3-min) (LW); and, sitting + half-hourly bouts of simple resistance activities for 3-min (SRA), each separated by 6-14 days washout. Resting seated BP was measured hourly (mean of 3 recordings, ≥20-min post-activity). Plasma noradrenaline was measured at 30-min intervals for the first hour after meals and hourly thereafter.

Results: Compared to SIT, mean resting systolic and diastolic BP were significantly reduced (P<0.001) for both LW (mean±SEM;-14±1/-8±1 mmHg) and SRA (-16±1/-10±1 mmHg), with a more pronounced effect for SRA (P<0.05 versus LW). Similarly, mean plasma noradrenaline was significantly reduced for both LW (-0.3±0.1 $nmol \cdot L^{-1}$) and SRA (-0.6±0.1 $nmol \cdot L^{-1}$) versus SIT, with SRA lower than LW (P<0.05). Mean resting heart rate was lowered by LW (-3±1 bpm; P<0.05), but not SRA (-1±1 bpm).

Conclusion: Interrupting prolonged sitting with brief bouts of LW or SRA reduces resting BP and plasma noradrenaline in adults with T2D, with SRA being more effective. Given the ubiquity of sedentary behaviors and poor adherence to structured exercise, this approach may have important implications for BP management in patients with T2D.

Key words: cardiovascular disease prevention, diabetes mellitus, hypertension-high blood pressure, sedentary lifestyle, physical activity

INTRODUCTION

Hypertension and type 2 diabetes (T2D) are common comorbidities that substantially increase the risk of both micro- and macro-vascular complications [1,2]. Indeed, when hypertension coexists with diabetes, the risk of cardiovascular disease is increased by some 75%, which further contributes to the overall morbidity and mortality of an already high-risk population [2]. As a frontline therapy and adjunct to pharmacotherapy, lifestyle interventions – including diet and exercise (30-60 min of continuous or accumulated exercise/day and resistance exercises at least 2-3 days/week) – remain cornerstones for improving blood pressure (BP), glucose and lipid control [3]. However, despite the known benefits, many with T2D remain physically inactive [4] and spend large amounts of time in sedentary behaviors (sitting) – defined as any sitting or reclining behavior during waking hours with low energy expenditure [(<1.5 Metabolic Equivalents [5,6]].

Sedentary behaviors (e.g. TV viewing, other screen time, driving) have been associated with higher resting BP [7] and the onset of hypertension [8,9] independent of moderate-vigorous physical activity, adiposity, age and other common risk factors. This is consistent with experimental studies demonstrating an elevation of BP across a 3-5 hour period of sitting, with concomitant increases in leg blood pooling and total peripheral resistance, as well as reductions in thigh blood flow and endothelial function [10,11]. In turn, there is observational and experimental evidence that regularly interrupting prolonged periods of sitting can be associated with a more favourable cardiometabolic risk profile compared to an equivalent amount of sitting time accumulated in longer, uninterrupted bouts [12-16]. Indeed, we recently showed that interrupting sitting time with brief intermittent walking bouts improves glycemic control in adults with T2D [15], and reduces resting BP in overweight/obese adults [17]. Whether the resting BP benefits extend to those with established cardiometabolic disease, such as T2D, remains

unknown. Furthermore, no study has examined the utility of interrupting sitting via brief bouts of simple resistance-type activities performed in a fixed position, an approach which may provide a potent metabolic or cardiovascular stimulus, and offer a pragmatic alternative during work tasks or leisure-pursuits where sitting time is frequently accrued.

Accordingly, we examined the effects of interrupting sitting time with brief bouts of light-intensity walking (LW) or simple resistance activities (SRA) on resting BP in adults with T2D. Given the known effects of exercise on BP and the sympathetic nervous system [18-20], concurrent changes in plasma noradrenaline (NA) were assessed to inform about this as a potential candidate mechanism. We hypothesized that resting BP and NA levels during prolonged sitting would be attenuated by brief (3 min) intermittent bouts of light-intensity physical activity.

METHODS

Participants

Non-smoking men and women [body mass index (BMI) 25-40 $kg \cdot m^2$)] aged 35-75 years with T2D (diet or Metformin-controlled, HbA1c 6.5-9%) were recruited. Participants were excluded if they self-reported sitting <5 hours/day and/or were meeting physical activity guidelines (≥150 minutes/week of moderate-intensity exercise). The study was approved by the Alfred Human Research Ethics Committee and all participants provided written informed consent.

Study design

This randomized crossover trial was undertaken at the Baker IDI Heart & Diabetes Institute between October 2013 and November 2014. Detailed screening and testing procedures have been described previously [15]. In brief, participants attended the

laboratory on five separate occasions: 1) medical screening visit; 2) familiarization visit; and 3-5) three acute trial condition visits in a randomized order, each separated by 6-14 days. Trial condition order was randomized by a third party (block-randomization and balanced block sizes) and stratified by gender. Power calculations were based on the co-primary outcomes (postprandial glucose and insulin responses following mixed meals) [15], with blood pressure a pre-specified secondary endpoint of the study. Participants underwent initial orientation to SRA and LW activities during screening and familiarization to ensure the activity interventions could be undertaken safely and consistently.

Experimental protocol

On trial condition days, participants arrived at the laboratory at 0715 h after a 12 h fast, having abstained from caffeine, alcohol, and structured moderate-vigorous physical activities (i.e., no physical activity beyond activities of daily living) for 48 h. Each trial condition (see Figure 1) commenced with a 60 min 'steady-state' period (-1 h to 0 h), after which participants consumed standardized breakfast (0 h) and lunch (3.5 h) meals, with the time taken to consume (<20 min per meal) replicated in subsequent conditions. An indwelling catheter was inserted into an antecubital vein at -1 h and a fasting (baseline) sample collected after the steady-state period at 0 h. Following this, postprandial samples were collected at 0.5, 1.0, 2.0, 3.5 (pre-lunch), and 4.0, 4.5, 5.5, and 7.0 h. Participants commenced the following experimental protocols after the breakfast meal: A) SIT: uninterrupted sitting; B) LW: sitting interrupted with 3 min bouts of light-intensity walking (3.2 $km \cdot h^{-1}$) every 30 min; and, C) SRA: sitting interrupted with 3 min bouts of simple resistance activities over 30 min (comprising 20 s body weight half-squats, 20 s calf raises, 20 s gluteal contractions and knee raises; repeated 3 times in sequential order while mimicking a standardized, pre-prepared video recording).

INSERT **FIGURE 1** ABOUT HERE

Meals were standardized between conditions and were individualized to each meet 33% of daily estimated energy requirements [21] (mean±SEM, 823±25 kcal/meal). The target macronutrient profile was 12-15% energy from protein, 55-58% from carbohydrate and 29-31% from fat. An evening meal pack was also provided for participants to prepare at home on the evenings prior to experimental conditions.

Participants sat upright in a comfortable chair throughout all experimental conditions and were instructed to minimize excessive movement, only rising from the chair to void. Standardized lavatory visits incorporated into the protocol minimized unscheduled physical activity; however, additional lavatory visits were permitted. Participants complied with the respective trial condition protocols under direct supervision from research staff. They had access to television, DVDs, books, magazines and internet services during the trial conditions. Participants completed each experimental trial condition in a private clinic room. They were permitted to check emails, but were asked to avoid potentially stimulating activities that may influence their BP, such as horror/suspense movies, computer gaming and/or gambling. Activity intensity during the trial conditions was monitored using heart rate (difference pre- versus post activity-bout) and the Borg Rate of Perceived Exertion (RPE; 6-20) scale. As previously reported, the difference for heart rate [immediately post-activity bout minus pre; mean±SEM (range: min-max)] for the LW and SRA activity-break conditions were 17±1.2 (8-31) and 19±1.0 (10-30) bpm, and for mean RPE was 9±0.3 (7–12) and 10±0.3 (7-13) points, respectively.

Blood pressure measurement and biochemical analysis

Resting BP and heart rate were measured in the seated upright position using an automated oscillometric blood pressure monitor (Digital Automatic Blood Pressure Monitor HEM-907, Omron, Kyoto, Japan). All measures were taken by trained research personnel, using an appropriately sized cuff. The same protocol for BP recordings applied at the initial screening/informed consent visit (i.e. average of three consecutive measures taken 1 min apart) was followed at each time point of each experimental condition (see Figure 1 for specific time points). The sequence of 3 measurements was always initiated 10 min before activity bouts. Measurements were taken on the same arm for all conditions, contralateral to the arm with the indwelling venous catheter (excepting 6 participants, for whom the alternate arm was used due to difficulties with the cannulation procedure).

Blood samples for plasma catecholamine determination were drawn into EGTA-glutathione tubes, centrifuged within 5 min of collection (2000 rpm for 15 min at 4°C), and the plasma stored at -80°C. Plasma NA concentrations were determined by high-performance liquid chromatography with coulometric detection, following extraction from plasma using alumina adsorption [22]. Recoveries of internal standard were used to adjust for loss during extraction. Intra-assay and inter-assay coefficients of variation were 1.3% and 3.8%, respectively. Assays for each individuals' three visits were completed in one assay run.

Statistical analyses

Generalized linear mixed models with random intercepts were used to evaluate the differential effects of the experimental conditions on the selected outcomes using Stata 12 (StataCorp LP). Residuals were examined for serial correlation, heteroscedasticity and normality. Substantial departures from model assumptions were not observed. A two-tail

probability level of 0.05 was adopted. Data are expressed as mean±SEM in text unless otherwise stated. Mean BP and plasma NA values (Figure 2; panels c, d and e) were quantified as the mean of all timepoints after 0 h. The difference between conditions represents the difference in these mean values by condition. All models were adjusted for potential covariates explaining residual outcome variance (age, BMI and gender), pre-prandial/baseline values (mean of timepoints -1 and 0 h for BP and heart rate outcomes, and timepoint 0 h for plasma NA) and period effects (treatment order). Time-by-condition and gender-by-condition interaction tests were performed for both BP and NA. Post-hoc analyses were also performed for each outcome to explore the potential influence of antihypertensive medications and baseline BP values.

RESULTS

Participant characteristics

Twenty-four participants [14 men, 10 women; mean±SD age, 62±6 years; BMI, 33.0±3.4 $kg{\cdot}m^{2}$; HbA1c, 7.2±0.7%; eGFR 87±8 $mL{\cdot}min^{-1.}1.73m^{-2}$; diabetes duration 6.8±5.1 years; n=23 taking metformin; n=15 taking statins] were randomized and completed all trial conditions. They were predominantly pre- or hypertensive (88%), with n=3 (12%) normotensive, n=4 (17%) pre-hypertensive, and n=17 (71%) hypertensive [23]. Participant attributes were comparable between genders for age, waist circumference and baseline BP/metabolic data, however BMI was significantly higher for women (mean±SD: 31.5±3.0 versus 35.2±2.8, $P<0.05$). All participants maintained their baseline anti-hypertensive treatment and other medications (Table 1) throughout the course of the trial.

INSERT **TABLE 1** ABOUT HERE

Resting BP, heart rate and plasma NA responses to prolonged and interrupted sitting

Mean systolic and diastolic BP and plasma NA data over time by trial condition are displayed in Figure 2 (panels a and b). Compared to SIT, both LW and SRA reduced mean resting systolic and diastolic BP (Figure 2, panels c and d; $P<0.001$), with the effect being more pronounced with SRA ($P<0.05$ versus LW). Similarly, compared to SIT, both LW and SRA were associated with significantly reduced mean plasma NA concentrations (Figure 2, panel e), with SRA lower than LW ($P<0.043$). Changes in mean plasma NA and mean systolic and diastolic BP were not significantly correlated ($P>0.05$, data not shown). A small but significantly lower mean resting heart rate was observed for LW only (SIT: 79±1; LW: 76±1; SRA: 78±1 bpm, $P<0.05$). Condition-by-time interaction effects were observed for both mean systolic and diastolic BP relative to the 1 h steady-state period (baseline BP). These demonstrated that during the SIT condition, BP was increased 10±1 / 5±1 mmHg ($P<0.001$) by the end of the day. Conversely, within-condition changes for LW and SRA indicated progressive reductions in systolic (-10±1 and -12±2 mmHg) and diastolic (-6±1 and -8±1 mmHg) BP by the end of the day (both $P<0.001$).

INSERT **FIGURE 2** ABOUT HERE

Gender, antihypertensive medications and baseline BP

A significant gender-by-condition interaction effect was observed for the mean difference in systolic BP between conditions SIT and SRA (Supplemental Figure S1); indicating that, while still significantly lower for both genders, the magnitude of the systolic BP reduction for SRA versus SIT was greater (↓15% versus ↓11%) in women than in men. Reductions in all BP and heart rate variables were not influenced by antihypertensive medications, however, the magnitude of the mean NA reduction was

significantly greater (↓6% versus ↓22%) for SRA compared to SIT in those taking antihypertensive medications (Supplemental Figure S1). Treatment with specific medications known to increase NA reflexively (i.e. diuretics and/or calcium channel blockers) was not associated with differential BP or plasma NA effects (i.e. vs. treatment with other antihypertensives and vs. no antihypertensive treatment. The magnitude of the difference in mean systolic BP with interrupted sitting tended to be greater in those participants with higher baseline systolic BP compared to those with lower baseline systolic BP; however, only the SRA-by-baseline systolic BP interaction was statistically significant (P=0.046 for SRA, P=0.076 for LW; Supplemental Figure S2). No significant interactions were observed for any other outcomes (non-significant data not reported).

DISCUSSION

The major novel finding of this study is that, in overweight/obese inactive men and women with T2D, interrupting prolonged sitting with brief intermittent bouts of either light-walking or simple resistance activities acutely reduced resting systolic and diastolic BP. This BP differential reflected both a progressive elevation in BP from baseline in the prolonged sitting condition and a progressive reduction in BP during the activity bout conditions. The BP-lowering effects on both activity days were paralleled by a significant reduction in plasma NA levels, although changes in systolic and diastolic BP and NA were not significantly correlated. Moreover, the magnitude of reductions in BP and NA were significantly greater with the simple resistance activities compared to the light walking. The present results extend recent findings in overweight/obese adults [17] by demonstrating the potential hypotensive effects of interrupting prolonged sitting in patients with T2D – which, if sustained, are comparable to that of monotherapy with many common anti-hypertensive drugs [24].

Evidence on the duration and intensity required for optimal BP reduction with accumulated activity bouts is limited, and less is known about the antihypertensive effects of even shorter (<10 min) bouts of light-intensity physical activity. Miyashita and colleagues showed that accumulating 30 min of brisk walking [25] or running [26] in 3 min bouts interspersed throughout the day was as effective as a 30 min continuous bout of similar intensity in reducing acute and second day systolic BP in young normotensive/pre-hypertensive men. Interestingly, the BP reduction observed for the intermittent running bout condition was no greater than walking bouts, despite increases in intensity and energy expended, which was similar to findings in sedentary adults [27]. It was also recently reported in overweight/obese adults that accumulating 2.5 h of standing or light-intensity physical activity during an 8-h workday equally improved ambulatory BP during and after work hours, compared to prolonged sitting [28]. These data and ours are congruent with previous literature regarding a light-intensity physical activity 'threshold' for blood pressure lowering [3,29], which may even be related to simple postural change. It is possible that the increased intensity and/or compound nature of the skeletal muscle contractile activity associated with the simple resistance activities evoked a stronger muscle pressor reflex, with greater post-activity vasodilatation in the absence of a compensatory increase in cardiac output, potentially contributing to lower NA and BP [30,31]. These factors, along with the optimal mode, frequency, duration and intensity of very short activity bouts for blood pressure control in T2D and hypertensive patients, should be examined in future studies.

Consistent with previous evidence on the influence of continuous exercise on BP-lowering [3], participants with higher baseline systolic BP generally showed a more pronounced reduction in systolic BP during the physical activity conditions, relative to prolonged sitting. The increased magnitude of BP reduction during the simple resistance

activity condition for women compared to men, while intriguing and consistent with epidemiological findings that have documented gender differences in the associations of television viewing time with cardiometabolic risk biomarkers [32,33], is challenging to explain. We did not observe significant changes in heart rate, oxygen consumption, perceived exertion or plasma NA levels (stratified data not reported) for women compared to men, which may have formed a plausible basis for these gender variations. It should also be noted that all women were post-menopausal (although not significantly older than the men) and were not taking hormone replacement therapy. Differences in adipose and lean body mass or other biological disparities between men and women with T2D could be the potential basis for gender differences.

The mechanisms accounting for the reported blood pressure reductions with interrupted versus uninterrupted sitting are likely to be multiple [3,34]. Lower sympathetic nerve activity is the most salient feature of post-exercise hypotension [18,19] which may contribute to reductions in both cardiac output and total peripheral resistance. A role for this mechanism is supported by our observation of reduced plasma NA levels during the activity bout conditions, although more direct indices of sympathetic nervous system activity would be required for definitive proof. Interestingly, any reductions in sympathetic nervous system activity may either be a direct consequence of the interrupted sitting intervention, or secondary to reductions in plasma insulin [15,35,36]. Further, evidence suggests that interruptions in sitting time may promote endothelial-dependent vasodilation via increased arterial shear stress secondary to activity-related blood flow and heart rate elevation [37,38]. Although direct measurements of blood flow, cardiac output and/or sympathetic activity would have compromised the present study design, such measures, or more sophisticated tracer techniques to address whether

neurotransmitter levels were a result of decreased clearance or increased release, would be highly informative in future studies.

Strengths of this study include: the well-controlled randomized cross-over study design, allowing for within and between participant comparisons and a smaller sample size; the standardized trial condition lead-in periods, with strict but pragmatic control of confounder variables such as diet, physical activity, and fasting metabolic levels; hourly blood pressure assessment using automated serial measurements; and, full retention of participants. The potential efficacy of an alternative, simple and practical form of sitting interruption (brief bouts of simple resistance activities) was also demonstrated, suggesting that the benefits associated with sitting interruptions may not be limited to only those involving ambulatory activities. Given the acute nature of this trial, we can only speculate on possible longer term exposures. It is also possible that the BP reductions observed in this study may be smaller if the sitting (control) condition was more reflective of free-living conditions. As such, assessment of ambulatory blood pressure over consecutive days under free-living scenarios would be an important next step. Finally, further research is needed to determine whether effects can be generalized to other populations – including the non-obese, pre-menopausal women, and less well-controlled T2D patients (i.e. insulin-dependent with beta cell dysfunction) – who may have differing levels of sympathetic activation; and, identify whether the approach we have tested is feasible and beneficial for those limited physically by diabetic complications or by other co-morbidities.

We have shown that interrupting prolonged sitting with brief light walking or simple resistance activity bouts acutely reduces resting BP and plasma NA levels in adults with T2D, most of whom were also hypertensive. Thus, interrupting prolonged sitting may be a practical strategy that could contribute towards minimizing the risk of micro- and

macrovascular complications in T2D patients. Although longer term efficacy needs to be established, our findings provide the first experimental evidence in T2D patients demonstrating the beneficial impact of interrupting prolonged sitting with brief intermittent activity bouts for blood pressure control. With these caveats in mind, we therefore propose that healthcare professionals consider advising their patients on regularly interrupting prolonged sitting time, in addition to promoting the well-established benefits of moderate-vigorous and leisure-time physical activity.

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REFERENCES

1. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. *Diabetes Care.* 2002;25:134-147.
2. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC, Holman RR. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ.* 2000;321:412-419.
3. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc.* 2004;36:533-553.
4. Zhao G, Ford ES, Li C, Mokdad AH. Compliance with physical activity recommendations in US adults with diabetes. *Diabet Med.* 2008;25:221-227.
5. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, Troiano RP. Amount of time spent in sedentary behaviors in the United States, 2003-2004. *Am J Epidemiol.* 2008;167:875-881.
6. Sedentary Behaviour Research Network. Standardized use of the terms "sedentary" and "sedentary behaviours". *Appl Physiol Nutr Metab.* 2012;37:540-542.
7. Lee PH, Wong FK. The association between time spent in sedentary behaviors and blood pressure: a systematic review and meta-analysis. *Sports Med.* 2015;45:867-880.
8. Beunza JJ, Martinez-Gonzalez MA, Ebrahim S, Bes-Rastrollo M, Nunez J, Martinez JA, Alonso A. Sedentary behaviors and the risk of incident hypertension: the SUN Cohort. *Am J Hypertens.* 2007;20:1156-1162.
9. Ragland DR, Greiner BA, Holman BL, Fisher JM. Hypertension and years of driving in transit vehicle operators. *Scand J Soc Med.* 1997;25:271-279.
10. Padilla J, Sheldon RD, Sitar DM, Newcomer SC. Impact of acute exposure to increased hydrostatic pressure and reduced shear rate on conduit artery endothelial function: a limb-specific response. *Am J Physiol Heart Circ Physiol.* 2009;297:H1103-1108.
11. Shvartz E, Gaume JG, White RT, Reibold RC. Hemodynamic responses during prolonged sitting. *J Appl Physiol.* 1983;54:1673-1680.
12. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, Owen N. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes Care.* 2008;31:661-666.
13. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. *Eur Heart J.* 2011;32:590-597.
14. Peddie MC, Bone JL, Rehrer NJ, Skeaff CM, Gray AR, Perry TL. Breaking prolonged sitting reduces postprandial glycemia in healthy, normal-weight adults: a randomized crossover trial. *Am J Clin Nutr.* 2013;98:358-366.
15. Dempsey PC, Larsen RN, Sethi P, Sacre JW, Straznicky NE, Cohen ND, Cerin E, Lambert GW, Owen N, Kingwell BA, Dunstan DW. Benefits for Type 2 Diabetes of Interrupting Prolonged Sitting With Brief Bouts of Light Walking or Simple Resistance Activities. *Diabetes Care.* 2016;39:964-972.
16. Dunstan DW, Kingwell BA, Larsen R, Healy GN, Cerin E, Hamilton MT, Shaw JE, Bertovic DA, Zimmet PZ, Salmon J, Owen N. Breaking up prolonged sitting reduces postprandial glucose and insulin responses. *Diabetes Care.* 2012;35:976-983.

17. Larsen RN, Kingwell BA, Sethi P, Cerin E, Owen N, Dunstan DW. Breaking up prolonged sitting reduces resting blood pressure in overweight/obese adults. *Nutr Metab Cardiovasc Dis.* 2014;24:976-982.
18. Floras JS, Sinkey CA, Aylward PE, Seals DR, Thoren PN, Mark AL. Postexercise hypotension and sympathoinhibition in borderline hypertensive men. *Hypertension.* 1989;14:28-35.
19. Floras JS, Senn BL. Absence of post exercise hypotension and sympathoinhibition in normal subjects: additional evidence for increased sympathetic outflow in borderline hypertension. *Can J Cardiol.* 1991;7:253-258.
20. Meredith IT, Friberg P, Jennings GL, Dewar EM, Fazio VA, Lambert GW, Esler MD. Exercise training lowers resting renal but not cardiac sympathetic activity in humans. *Hypertension.* 1991;18:575-582.
21. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr.* 1985;39 Suppl 1:5-41.
22. Lambert GW, Jonsdottir IH. Influence of voluntary exercise on hypothalamic norepinephrine. *J Appl Physiol (1985).* 1998;85:962-966.
23. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003;289:2560-2572.
24. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ.* 2009;338:b1665.
25. Miyashita M, Burns SF, Stensel DJ. Accumulating short bouts of brisk walking reduces postprandial plasma triacylglycerol concentrations and resting blood pressure in healthy young men. *Am J Clin Nutr.* 2008;88:1225-1231.
26. Miyashita M, Burns SF, Stensel DJ. Accumulating short bouts of running reduces resting blood pressure in young normotensive/pre-hypertensive men. *J Sports Sci.* 2011;29:1473-1482.
27. Coleman KJ, Raynor HR, Mueller DM, Cerny FJ, Dorn JM, Epstein LH. Providing sedentary adults with choices for meeting their walking goals. *Prev Med.* 1999;28:510-519.
28. Zeigler ZS, Mullane SL, Crespo NC, Buman MP, Gaesser GA. Effects of Standing and Light-Intensity Activity on Ambulatory Blood Pressure. *Med Sci Sports Exerc.* 2016;48:175-181.
29. Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L. The acute versus the chronic response to exercise. *Med Sci Sports Exerc.* 2001;33:S438-445; discussion S452-433.
30. Fowler RM, Maiorana AJ, Jenkins SC, Gain KR, O'Driscoll G, Gabbay E. A comparison of the acute haemodynamic response to aerobic and resistance exercise in subjects with exercise-induced pulmonary arterial hypertension. *Eur J Prev Cardiol.* 2013;20:605-612.
31. Gielen S, Schuler G, Adams V. Cardiovascular effects of exercise training: molecular mechanisms. *Circulation.* 2010;122:1221-1238.
32. Dunstan DW, Salmon J, Owen N, Armstrong T, Zimmet PZ, Welborn TA, Cameron AJ, Dwyer T, Jolley D, Shaw JE. Physical activity and television viewing in relation to risk of undiagnosed abnormal glucose metabolism in adults. *Diabetes Care.* 2004;27:2603-2609.

33. Thorp AA, Healy GN, Owen N, Salmon J, Ball K, Shaw JE, Zimmet PZ, Dunstan DW. Deleterious associations of sitting time and television viewing time with cardiometabolic risk biomarkers: Australian Diabetes, Obesity and Lifestyle (AusDiab) study 2004-2005. *Diabetes Care.* 2010;33:327-334.
34. Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. *Hypertension.* 1993;22:653-664.
35. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation.* 2006;113:1888-1904.
36. Huggett RJ, Scott EM, Gilbey SG, Stoker JB, Mackintosh AF, Mary DA. Impact of type 2 diabetes mellitus on sympathetic neural mechanisms in hypertension. *Circulation.* 2003;108:3097-3101.
37. Thosar SS, Bielko SL, Mather KJ, Johnston JD, Wallace JP. Effect of prolonged sitting and breaks in sitting time on endothelial function. *Med Sci Sports Exerc.* 2015;47:843-849.
38. Morishima T, Restaino RM, Walsh LK, Kanaley JA, Fadel PJ, Padilla J. Prolonged sitting-induced leg endothelial dysfunction is prevented by fidgeting. *Am J Physiol Heart Circ Physiol.* 2016;311:H177-182.

FIGURE LEGENDS

Figure 1. Experimental day protocol for each trial condition with meal consumption and measurement time-points. Thick vertical lines in the grey bars for conditions B and C show the timing of the light-walking (LW) and simple resistance activity (SRA) interruptions from uninterrupted sitting (SIT). The vertical striped section in the grey bars from -1 to 0 h denotes the sitting 'steady-state' period. Blood pressure and blood collection were recorded at 10 min and 1 min prior to activity bouts, respectively, during the LW and SRA conditions.

Figure 2. The effect of uninterrupted sitting (SIT), and sitting interrupted with 3-min light-intensity walking (LW) and simple-resistance activity (SRA) bouts on mean±SEM resting systolic (SBP) and diastolic (DBP) blood pressure (a) and plasma noradrenaline (NA) (b) levels over time. Panels c, d and e represent marginal means±SEM (i.e. averaged values for all timepoints after 0 h, adjusted for age, BMI, gender, fasting levels, and treatment order) for SBP, DBP and plasma NA per condition, respectively. Vertical dashed lines in panels a and b indicate the timing of the breakfast (0 h) and lunch (3.5 h) meals. Values within the bars (panels c, d and e) denote to the mean mmHg or percentage change compared to SIT. *Difference from SIT (P<0.05). †SRA different from LW (P<0.05).

Table 1. Participant clinical characteristics and medications

Metabolic and cardiovascular risk factors	
Systolic blood pressure (mmHg)	123 ± 14
Diastolic blood pressure (mmHg)	77 ± 9
Fasting total cholesterol ($mmol \cdot L^{-1}$)	4.4 ± 0.8
Fasting LDL-cholesterol ($mmol \cdot L^{-1}$)	2.5 ± 0.8
Fasting HDL-cholesterol ($mmol \cdot L^{-1}$)	1.1 ± 0.3
Fasting triglycerides ($mmol \cdot L^{-1}$)	1.9 ± 1.0
Fasting glucose ($mmol \cdot L^{-1}$)	8.2 ± 1.4
Concomitant medications	
Metformin	23 (96%)
Statin	15 (63%)
Anti-depressants (SSRI or SNRI)	4 (17%)
Anti-hypertensive	16 (67%)
ACE inhibitor or ARB	16 (67%)
Calcium channel blocker	5 (21%)
Beta blocker	2 (8%)
Thiazide diuretic	11 (46%)

Data are mean±SD or number (%). SSRI, Selective serotonin reuptake inhibitor; SNRI, Serotonin and norepinephrine reuptake inhibitor; ACE, Angiotensin converting enzyme; ARB, Angiotensin II receptor blocker. Note: blood pressure measurements were collected during the screening visit. Fasting metabolic measurements were collected at the beginning of the first trial condition.

Figure 1

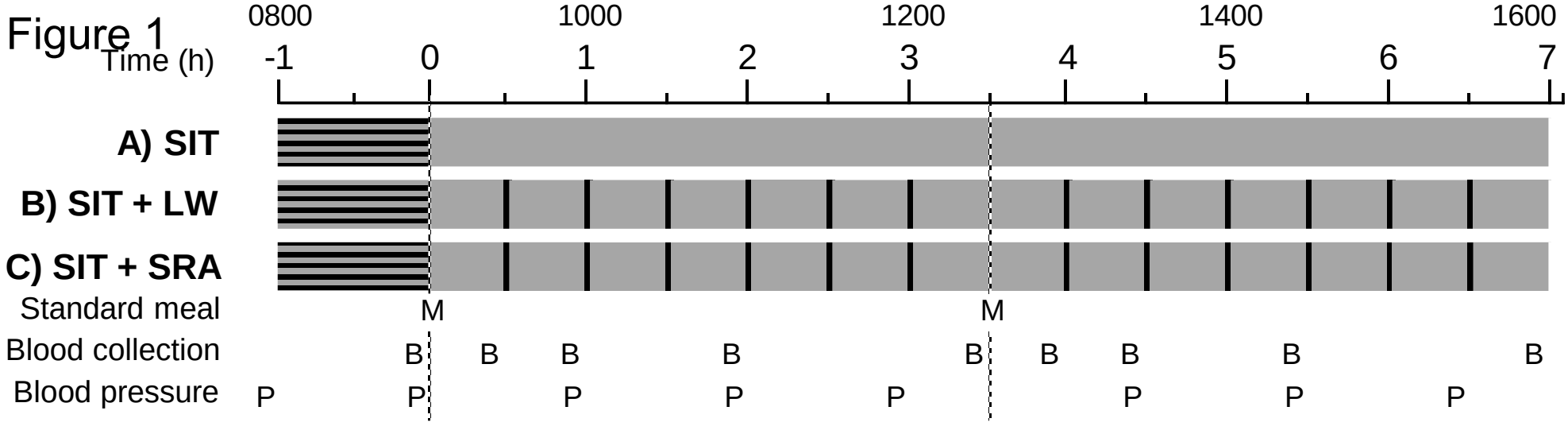
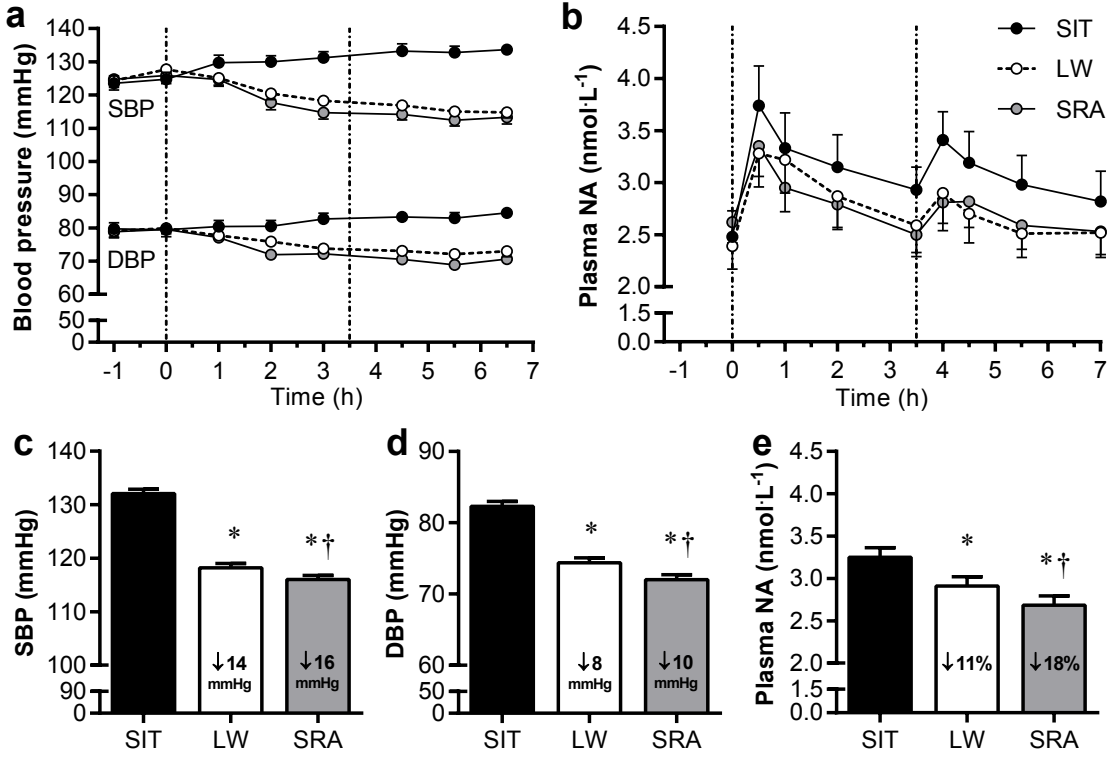

0800
1000
1200
1400
1600
Time (h)
-1
0
1
2
3
4
5
6
7
A) SIT
B) SIT + LW
C) SIT + SRA
Standard meal
Blood collection
Blood pressure
M
M
B
P

Figure 2


a
Blood pressure (mmHg)
SBP
DBP
Time (h)
b
Plasma NA (nmol·L-1)
SIT
LW
SRA
Time (h)
c
SBP (mmHg)
↓14 mmHg
↓16 mmHg
SIT
LW
SRA
d
DBP (mmHg)
↓8 mmHg
↓10 mmHg
SIT
LW
SRA
e
Plasma NA (nmol·L-1)
↓11%
↓18%
SIT
LW
SRA