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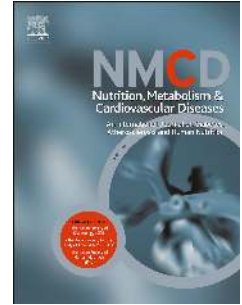
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Title: Breaking up prolonged sitting reduces resting blood pressure in overweight/obese adults

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ABSTRACT

Aim: To compare the effect of 7 hours of prolonged sitting on resting blood pressure with a similar duration of sitting combined with intermittent brief bouts of light-intensity or moderate-intensity physical activity.

Methods and Results: Overweight/obese adults (n = 19; aged 45-65 years) were recruited for a randomized three-treatment crossover trial with a one-week washout between treatments: 1) uninterrupted sitting; 2) sitting with 2 minute bouts of light-intensity walking at 3.2km/hr every 20 minutes; and, 3) sitting with 2 minute bouts of moderate-intensity walking at between 5.8-6.4km/hr every 20 minutes. After an initial 2 hour period seated, participants consumed a test meal (75g carbohydrate, 50g fat) and completed each condition over the next 5 hours. Resting blood pressure was assessed oscillometrically every hour as a single measurement, 5 minutes prior to each activity bout. GEE models were adjusted for sex, age, BMI, fasting blood pressure and treatment order.

After adjustment for potential confounding variables, breaking up prolonged sitting with light and moderate-intensity activity breaks was associated with lower systolic blood pressure [light: 120 ± 1mmHg (estimated marginal mean ± SEM), P=0.002; moderate: 121 ± 1mmHg, P=0.02], compared to uninterrupted sitting (123 ± 1mmHg). Diastolic blood pressure was also significantly lower during both of the activity conditions (light: 76 ± 1mmHg, P=0.006; moderate: 77 ± 1mmHg, P=0.03) compared to uninterrupted sitting (79 ± 1mmHg). No significant between-condition differences were observed in mean arterial pressure or heart rate.

Conclusion: Regularly breaking up prolonged sitting may reduce systolic and diastolic blood pressure.

Trial Registration Number: ACTRN12609000656235 (http://www.anzctr.org.au)

INTRODUCTION

Regular physical activity is a well-accepted approach for the primary prevention of hypertension and is recommended as an adjunct to pharmacotherapy for the secondary prevention of cardiovascular disease.[1, 2] However, emerging evidence suggests that another set of behaviors, involving prolonged sitting, can adversely affect blood pressure (BP) even when meeting physical activity guidelines. Cross-sectional observations indicate positive associations of common sedentary behaviors (TV viewing or screen time) with BP, independent of traditional risk factors [e.g., age, alcohol intake, smoking and body mass index (BMI)] and leisure-time physical activity or cardiorespiratory fitness.[3, 4] Hypertension rates also increase as a function of exposure to sedentary behaviors (e.g., computer usage and driving),[5, 6] suggesting that reducing sedentary time may have implications for hypertension prevention and management.

Accumulating evidence suggests that a single continuous period of prolonged sitting may be more deleterious to health than sitting that is accumulated in shorter bouts (interrupted sitting). In a study of healthy individuals, 5 hours of uninterrupted sitting increased diastolic and mean arterial BPs (by 6 and 7.3mmHg, respectively) relative to measurements taken at 1 hour.[7] Furthermore, 60 minutes of sitting was required to achieve a hemodynamic steady-state, as cardiac output, calf pooling and thigh blood flow varied for up to an hour following standing and light walking or recumbency.[7] After 1 hour of sitting, cardiac output remained unchanged and total peripheral resistance increased,[7] suggesting that the BP rise may be secondary to candidate mechanisms involved in total peripheral resistance (ie. endothelial function, renin angiotensin system, autonomic activity). This suggests that frequently breaking up sitting time (either by changing posture or walking) may disturb the hemodynamic and potentially hypertensive effects of prolonged sitting. This is consistent

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with epidemiological evidence that suggests that breaks in sedentary time are beneficially associated with cardiometabolic variables, independent of total sedentary time and moderate-to-vigorous physical activity.[8] Therefore, we hypothesized that breaking up prolonged sitting with short bouts of walking would reduce BP, relative to uninterrupted sitting. In a controlled experimental setting, BP responses to 5 hours of prolonged sitting were compared with 5 hours of sitting that included either intermittent bouts of light-intensity physical activity (LIPA) or moderate-intensity physical activity (MIPA).

METHODS

Participants. Participants (n=19) were non-smokers, aged 45-65 years, with a BMI of 25-45 kg/m^2, and were excluded if they were taking glucose- or lipid-lowering medications or met current physical activity guidelines.[9] Written informed consent was obtained from all participants and the study was approved by the Alfred Hospital's Ethics Committee.

Study design. Conducted in a supervised laboratory setting at Baker IDI Heart and Diabetes Institute (Melbourne, Australia), this trial was undertaken between April 2009 and August 2010. The randomized crossover study involved three acute testing conditions, each separated by a week. The treatment order was stratified by sex and was randomly determined by a third party. Primary outcomes were postprandial blood glucose and insulin responses following a mixed meal, and were the basis of power calculations.[10] BP was a predefined secondary endpoint of the study.

*Experimental condition*s. Participants refrained from exercise, alcohol and caffeine, for 48 hours prior to each trial condition. On testing days, participants reported to the laboratory between 0700 and 0800 hour, having fasted overnight. Each testing day commenced with a 2

hour steady-state period, during which time participants remained seated. Following the steady-state phase, participants consumed a mixed meal (75 grams maltodextrin, 50 grams fat) and commenced one of the following protocols over the next 5 hours: 1) uninterrupted sitting; 2) sitting with 2 minute bouts of light-intensity walking on a motorized treadmill (level surface) at 3.2 km/hr every 20 minutes (the light-intensity physical activity breaks condition; LIPA); and 3) sitting with 2 minute bouts of moderate-intensity walking on a motorized treadmill (level surface) at between 5.8-6.4 km/hr every 20 minutes (the moderate-intensity physical activity breaks condition; MIPA). The speed of the treadmill during the moderate condition corresponded to a Borg relative perceived exertion rating between 12-14 determined from the participant's familiarization visit. On all testing days, participants sat upright in a comfortable lounge chair and and were prohibited from reclining to a semi-recumbent position. Participants had access to a television and reading materials (newspapers and magazines) and were instructed to minimize excessive movement during conditions. Toilet breaks were permitted when necessary.

Blood pressure measurements. All participants had their BP measured at the initial informed consent appointment, approximately 1 week before randomization. BP was measured 3 times in a clinic setting by the research nurse, using an automated oscillometric BP monitor (SureSigns VS3, Phillips, Eindhoven, The Netherlands). Participants were divided into 3 subgroups based on either a previous diagnosis of hypertension or the JNC-7 BP classifications:(i) normotensives: systolic BP <120 mmHg and diastolic BP: <80 mmHg; (ii) prehypertensives: $120 \geq$ systolic BP < 140 mmHg or $80 \geq$ diastolic BP < 90 mmHg; (iii) hypertensives: systolic BP $\geq$ 140 mmHg or diastolic BP: $\geq$ 90 mmHg.[11]

During the experimental conditions, resting brachial artery BP and heart rate were measured hourly by the research nurse as a single measurement, 5 minutes prior to each activity bout with the automated oscillometric BP monitor. Measurements were taken in a seated upright position on the arm contralateral to the arm with an intravenous indwelling cannula (for determination of blood glucose and insulin concentrations). Measurements were taken on the same arm for all conditions; however in exceptional circumstances (i.e., difficulties with cannulation procedure, n=2) the alternate arm was used.

Statistical analyses. All statistical analyses were performed using STATA statistical software (StataCorp LP, Texas, USA). Generalized estimating equations, with exchangeable working correlation to account for dependency in the data (repeated measures), were used to compare BPs (overall means) for each condition. All models were adjusted for potential covariates explaining residual outcome variance (age, sex and BMI), fasting BP values, and period effects (treatment order). Post hoc analyses were also performed to account for the effect of BP medications and the baseline BP classification. Participants were stratified into groups according to whether their baseline BP was within the normal range. Blood pressure measurements were considered "normal" if systolic and diastolic BPs were less than 120mmHg and 80mmHg, respectively, and were considered "sub-optimal" if they were more than 120mmHg and 80mmHg (which is inclusive of the JNC-7 classification for prehypertensive and hypertensive individuals).[11] Data are reported as means or marginal means ± SEM, where specified. A level of $P<0.05$ was considered significant.

RESULTS

Participant characteristics. Attributes of study participants and concomitant medications are shown in **Table 1**. With the exception of BMI and waist circumference, clinical

characteristics were within normal ranges. This study involved normotensive, prehypertensive and hypertensive participants, with normotensive individuals comprising almost half of the study cohort. Three, who were previously being treated for hypertension, maintained their baseline treatment regimen during the course of the trial.

Effects of interrupting sitting on BP. Both systolic and diastolic BP's increased during the steady-state period for all conditions. Systolic BP (SBP) continued to rise in the uninterrupted sitting condition and peaked at 1 hour after consumption of the test meal. In contrast, BPs decreased following the meal and the commencement of the activity protocols (**Figure 1a**). When all potential determinants (treatment, age, sex, BMI, starting BP and treatment order) were included in the statistical model, significant differences in regression parameters were observed for SBP (Wald chi-square statistic = 426, P<0.001) and DBP (Wald statistic = 719, P<0.001). The model revealed differences between treatments, with LIPA and MIPA breaks reducing SBP to a similar extent [light: 120 ± 1 mmHg (estimated marginal means ± SEM), *P*=0.002, effect size=0.61; moderate: 121 ± 1 mmHg, *P*=0.02, effect size=0.48] compared to uninterrupted sitting [123 ± 1mmHg] (**Figure 1b**). Diastolic BP (DBP) also decreased with both activity conditions (light: 76 ± 1 mmHg, *P*=0.006, effect size=0.68; moderate: 77 ± 1 mmHg, *P*=0.03, effect size=0.55) relative to uninterrupted sitting (79 ± 1 mmHg) (**Figure 1d**). No significant treatment differences were observed in mean arterial pressure or heart rate. The findings of a sensitivity analysis, which excluded those on antihypertensive therapy, did not affect the SBP results reported above. However, the difference in DBP was no longer statistically significant between the light and the uninterrupted sitting condition (*P*=0.16) when treated participants (n = 3) were removed from the analysis.

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Treatment effect according to baseline BP classification In those with hypertension and prehypertension (n=10), significant differences between regression parameters were observed for both SBP (Wald Chi-square=153, *P*<0.001) and DBP (Wald Chi-square=370, *P*<0.001). With regards to treatment effects, only the LIPA breaks condition lowered SBP and DBP (SBP: 129 ± 2 mmHg and DBP: 84 ± 1 mmHg, respectively) relative to the uninterrupted sitting condition (SBP: 133 ± 2 mmHg, *P*=0.009, effect size=0.46; DBP: 87 ± 1 mmHg, *P*=0.002, effect size=0.65), as the moderate-intensity condition was not significantly different from the sitting condition (moderate SBP: 131 ± 2 mmHg, *P*=0.22, effect size=0.25; moderate DBP: 85 ± 1mmHg, *P*=0.12, effect size=0.37). In the normal BP group (n=9), the statistical model (SBP: Wald Chi-square=131, *P*<0.001; DBP: Wald Chi-square=117, *P*<0.001) revealed no differences between treatments. However, there was a trend for LIPA and MIPA breaks to reduce SBP (light: 111 ± 1 mmHg, *P*=0.067, effect size=0.46; moderate: 111 ± 1 mmHg, *P*=0.056, effect size=0.47) when compared to the uninterrupted sitting condition (113 ± 1 mmHg). Activity protocols had no effect on DBP (light: 69 ± 1 mmHg, *P*=0.38, effect size=0.17; moderate: 69 ± 1mmHg, *P*=0.07, effect size=0.36) compared to uninterrupted sitting (70 ± 1mmHg).

DISCUSSION

Interrupting sitting time with either LIPA or MIPA bouts of walking significantly lowered SBP by 2-3mmHg and DBP by 2mmHg, relative to uninterrupted sitting. Furthermore, the BP decrease was not dose-related to the intensity level of the breaks, providing support to earlier findings that breaks in sedentary time per se are beneficially associated with cardiometabolic risk biomarkers.[8] By means of extrapolation based on the existing evidence, a sustained SBP drop of this magnitude could reduce the relative risk of stroke mortality by 6-8%, of coronary artery disease by 4-5%, and of all-cause mortality by 3-4%.[1] Our findings suggest that

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breaking up sitting time, even with light-intensity breaks, may have clinical implications for overweight and obese individuals, particularly those who are highly sedentary and for whom light-intensity breaks may be more tolerable than breaks that are at a higher intensity.

The crossover study design allowed us to directly compare the BP effects of all three experimental protocols in the same individuals, eliminating the potential for inter-individual variability. The most striking difference was observed between conditions in SBP at 1 hour, as SBP rose beyond the steady-state period in the sitting condition and decreased following the commencement of the activity protocols. Contrary to earlier investigations which showed that sitting for 5 hours increased BP over time,[7] our study showed that SBP decreased at 2 hours post-meal, possibly due to concurrent peaks in glucose and insulin at this time. As described elsewhere,[10] the uninterrupted sitting condition was associated with a 24-29% higher post-meal glucose AUC and a 23% higher insulin AUC, compared with the activity protocols. Furthermore, insulin levels peaked 2 hours post-meal and were highest in the uninterrupted sitting condition. Although we did not examine potential underlying mechanisms, a plausible hypothesis is that the BP decrease in the uninterrupted sitting condition at this time could reflect an insulin-mediated vasodilatory effect[12] or a potentiating effect of the high carbohydrate, high fat meal on factors relating to postprandial hypotension.[13] In contrast, BP fell in the two active conditions following the commencement of the activity breaks. Exercise-induced hypotension may be relevant and reflects the functional product of changes in systemic vascular resistance and cardiac output, both of which may be affected by changes in body temperature, vasoactive substances (including nitric oxide), autonomic activity and blood volume shifts from the arterial to the venous system.[14] Therefore, it is likely that a complex interplay of mechanisms may account for the differences in BP observed in the current study.

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Breaking up sitting time reduced BP in an overweight and obese cohort, consisting of normotensive, prehypertensive and hypertensive individuals. As an individual's response to the activity bouts or prolonged sitting may vary according to their baseline BP diagnosis, we stratified the data according to normotensive or suboptimal BP classifications. We found that breaks in sitting time significantly lowered BP only in those with suboptimal BP, which is consistent with previous evidence demonstrating a more pronounced BP drop with continuous exercise in hypertensive patients compared to those who were normotensive.[15] However, only the LIPA breaks, and not MIPA breaks, reduced SBP and DBP in the suboptimal BP group. One possible explanation could be that LIPA and MIPA elicit different cardiovascular responses, as BP increases with intensity level during exercise. Another likely explanation is that small sample sizes in the subgroup analysis limited our ability to detect treatment differences. It is well known that obesity is an important risk factor for the future incidence of hypertension[16] and for the progression of prehypertension to hypertension.[17] Moreover, the association between BMI and arterial pressure occurs not only for obese hypertensive subjects, but also extends to non-obese, normotensive individuals.[18] Therefore, it is possible that advocating appropriate lifestyle modifications, such as breaking up prolonged sitting, earlier than clinically indicated may provide some benefit to overweight and obese individuals.

The impact of breaking up prolonged sitting in those who are hypertensive or pre-hypertensive has not been examined. However, indirect support for the possible merits of reducing sedentary time may be inferred from interventions that target increasing lifestyle physical activity, defined as the incorporation of short bouts of moderate-intensity activities into the daily routine.[19] Long-term randomized trials comparing lifestyle physical activity with structured exercise programs have demonstrated equivalent reductions in SBP and DBP previously inactive individuals.[20] In an acute outpatient setting, lifestyle physical activity

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significantly reduced ambulatory SBP for 6 hours in pre-hypertensive and 8 hours in hypertensive individuals compared to when the same individuals completed an inactive condition.[21] Importantly, the use of accelerometers in the study revealed that the participants incorporated mainly LIPA (as energy expenditure did not exceed 3.5 kCal·min-1) during the lifestyle condition. This suggests that incorporating short bouts of LIPA in the real-life setting may have similar BP effects to those seen in our study.

Public health guidelines for hypertension and pre-hypertension currently state that 30 minutes of MIPA can be accumulated throughout the day in bouts greater than 10 minutes.[1, 22] However, few studies have examined if shorter bouts of accumulated exercise can improve BP. In a randomized cross-over study involving healthy men, Miyashita et al[23] compared the acute and second day effects of one 30 minute continuous bout of brisk walking, ten 3 minute bouts of brisk walking and a rest period (no exercise). Resting SBP was 6-7% lower throughout day 2 for the accumulated and continuous protocols than on the day of complete rest. Coleman et al[24] also found equivalent improvements in BP following three activity programs where brisk walking was accumulated on 6 days/week as either a single 30 minute continuous bout, three 10 minute bouts or 30 minutes of bouts lasting 5 minutes or more. The minimal amount of time/bout that is required to benefit health is thus unclear. However, our study showed that as little as 2 minutes per bout might be sufficient to produce acute changes in BP.

From a public health viewpoint, breaking up sitting time with LIPA bouts may be readily incorporated into a variety of settings, including the workplace and domestic environments. LIPA is manifested in typical domestic and occupational tasks such as standing, ironing, cooking and casual walking. Several studies have demonstrated that sedentary time has a

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strong inverse association with LIPA (r=-0.96), whereas moderate-to-vigorous physical activity is only weakly associated.[25] Given that less than 5% of waking hours are spent in moderate-to-vigorous physical activity,[26] shifting the sedentary-light balance in favor of LIPA may have important implications for human health.

The potential health effects of LIPA are not widely documented, largely because of practical problems associated with quantifying spontaneous low-level movement. However, this has largely been overcome with the recent use of accelerometers and inclinometers. Observational studies that have employed these technologies have frequently demonstrated that LIPA is beneficially associated with a number of health markers.[25, 27] A recent cross-sectional study showed that accelerator-measured LIPA was a significant independent predictor of both SBP and DBP in men (explaining 16% and 22% of the variance respectively) and DBP in women.[28] The minimum amount of LIPA required to accrue health benefits is yet to be determined. In normotensive individuals, low-intensity walking for 1 hour on 5 days/week has been shown to reduce BP by 3/2mmHg, relative to a period of sedentary behavior, which is equivalent to the BP decreases seen with the LIPA and MIPA breaks in our study.[29] Meanwhile, other studies suggest that 30 minutes of LIPA is as effective as the same duration of moderate-intensity exercise for reducing BP in hypertensive individuals.[30] This is comparable to our study if we consider our findings in terms of the total activity time (sum of all activity bouts was 28 minutes).

This study had several limitations. First, BP was measured each hour as a single measurement (rather than serial measurements). However, as measurements were performed under constant conditions, we posit that averaging BP values over each treatment condition addresses the problem of lack of precision with single measurements. Second, we suspect that the limited

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numbers in the subgroup analysis hindered our ability to detect between treatment differences. Other considerations include unblinding of research personnel and participants to the treatment condition (although BP measures were automated), and the possible confounding influence of posture (independent of physical activity) and antihypertensive medications.

In conclusion, this study showed that regularly interspersing activity breaks during prolonged sitting time lowered resting BP. Further investigations are warranted to determine the chronic effect of breaking up sitting time in a various population groups (normotensive, prehypertensive and hypertensive), as well as the feasibility of such strategies in the general community, and the possible causal nature of the association between prolonged sitting and BP.

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Declaration of Conflicting Interests: None declared.

Author Contributions: DWD, BAK, EC, RNL and NO were involved in the concept and design of the study. RNL collected data and managed the trial. PS and EC were responsible for the statistical analysis of the data. Drafting of the manuscript for important intellectual content was done by RNL, BAK, NO and DWD and final revisions were done by PS and EC. DWD obtained funding and provided advice and supervision of the project.

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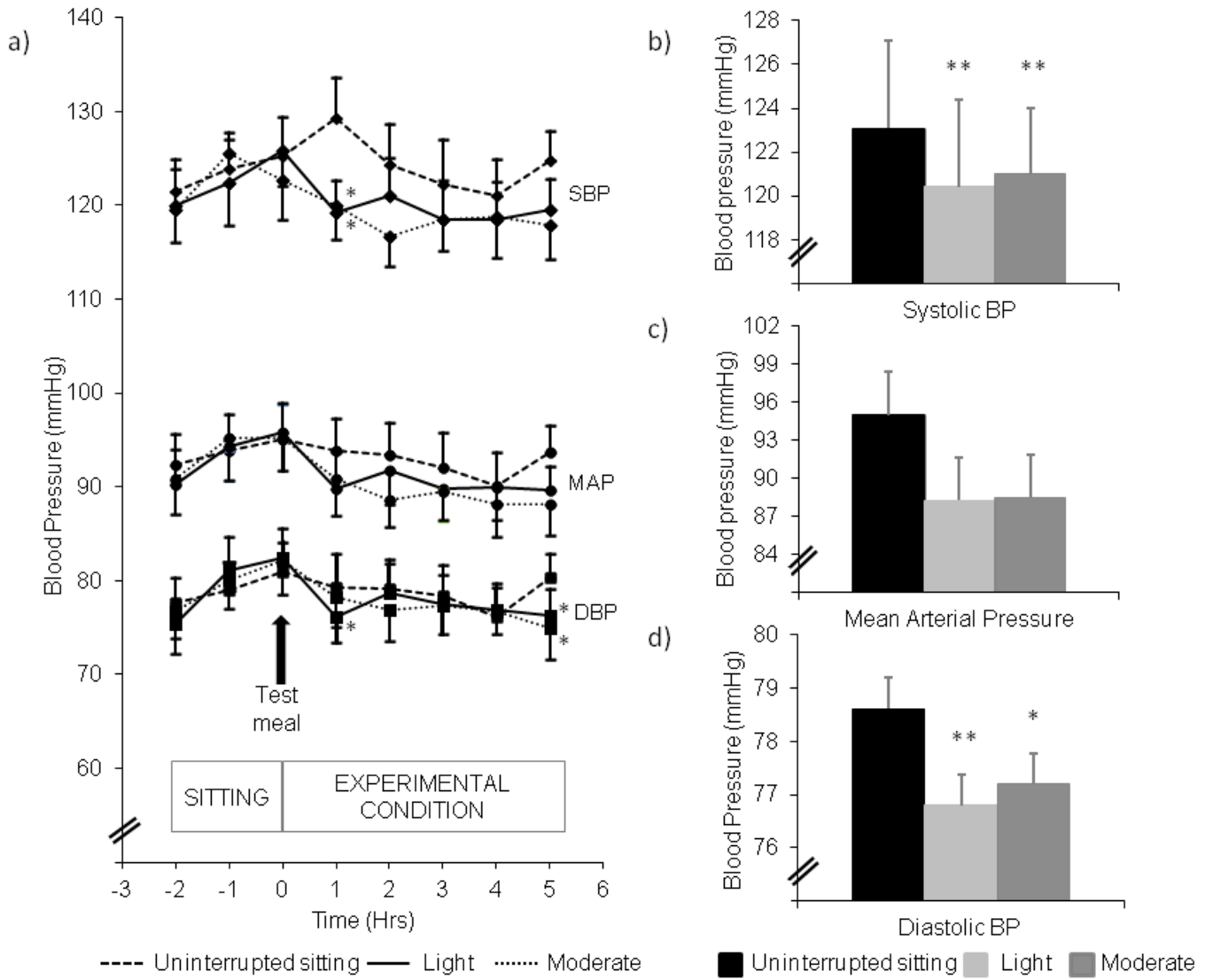
FIGURE 1

(a) Represents unadjusted mean blood pressure profiles during the steady-state and physical activity protocols. **(b-d)** Represent the overall marginal means (adjusted for age, sex, BMI, fasting BP, and treatment order) and error bars SEM for each condition.

**Significantly different from uninterrupted sitting condition, $P < 0.01$.

*Significantly different from uninterrupted sitting condition, $P < 0.05$.

Table 1: Participant characteristics

Demographics	
Age, yr	53.8 (1.1)[a]
Male No. (%)	11 (58%)
Concomitant medications, n (%)	
ACE inhibitor or ARB	1 (5%)
ACE inhibitor plus calcium channel blocker	2 (11%)
Proton pump inhibitor	2 (11%)
Short-acting bronchodilator	1 (5%)
Long-acting bronchodilator plus corticosteroid	1 (5%)
Estradiol – gel	1 (5%)
Antispasmodic medication	1 (5%)
Anthropometrics	
BMI, kg/m^2	31.2 (0.9)
Waist circumference, cm	105.6 (3.2)
Cardiovascular disease risk factors	
Blood pressure classification[b], n (%)	
Normotensive	9 (47%)
Prehypertensive	5 (26%)
Hypertensive	5 (26%)
Systolic blood pressure, mmHg	125 (3)
Diastolic blood pressure, mmHg	81 (2)
Total cholesterol, mmol/l	5.27 (0.26)

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LDL cholesterol, mmol/l	3.47 (0.22)
HDL cholesterol, mmol/l	1.07 (0.04)
Triacylglycerol, mmol/l	1.61 (0.18)

[a]Data are expressed as means (SEM) or number (%) where specified.

[b]Blood pressure classifications were based the average of three measurements taken at the screening visit or if the participant was previously diagnosed with hypertension.

Abbreviations: ACE, Angiotensin Converting Enzyme; ARB, Angiotensin II Receptor Blocker

a)

b) Systolic BP

c) Mean Arterial Pressure

d) Diastolic BP

---- Uninterrupted sitting —— Light ·········· Moderate

■ Uninterrupted sitting ■ Light ■ Moderate