Sedentary Behavior and Cardiovascular Disease Risk: Mediating Mechanisms

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CARTER, S., Y. HARTMAN, S. HOLDER, D.H. THIJSSEN, and N. HOPKINS. Sedentary behavior and cardiovascular disease risk: mediating mechanisms. *Exerc. Sport Sci. Rev.*, Vol. 45, No. 2, pp. 80–86, 2017. *Sedentary behavior has a strong association with cardiovascular disease (CVD) risk, which may be independent of physical activity. To date, the mechanism(s) that mediate this relationship are poorly understood. We hypothesize that sedentary behavior modifies key hemodynamic, inflammatory, and metabolic processes resulting in impaired arterial health. Subsequently, these vascular impairments directly and indirectly contribute to the development of CVD.* **Key Words:** sitting, physical activity, vascular function, shear stress, cardiovascular risk factors

Key Points

- Sedentary behavior (SB: *i.e.*, sitting, lying) is associated with numerous negative health connotations. Previous work has predominantly focused on the relationship between SB and all-cause mortality and/or metabolic disorders, yet the relationship between SB and the development of cardiovascular disease (CVD) has received less attention.
- Recent evidence suggests that the negative effects of SB on markers of vascular health, and, to a lesser degree, traditional CVD risk factors, are likely responsible for the increased CVD incidence and mortality associated with SB.
- We propose that SB-induced downregulation of shear rate and blood flow as well as alterations to glucose metabolism and inflammatory and oxidative stress pathways are likely to play a key role in the vascular dysfunction associated with SB.

INTRODUCTION

Physical activity (PA) relates to any bodily movement that is associated with energy expenditure and covers the entire spectrum from moderate- or vigorous-intensity activities (typically referred to as exercise) to low-intensity activities (*i.e.*, walking, daily life activities). The benefits of regular engagement in low, moderate, and/or vigorous PA have been apparent for some decades and have been frequently described in relation to primary and secondary prevention of cardiovascular disease (CVD). The importance of PA in the context of CVD risk reduction was first highlighted in a seminal study by Morris *et al.* (26), who observed that bus drivers experienced more than double the amount of CVD incidence than bus conductors. The authors speculated that the additional PA undertaken by the bus conductors reduced the risk for future development of CVD. This hypothesis has since been confirmed repeatedly when examining the contribution of PA to CVD morbidity and mortality, culminating in a recent estimate that suggests that physical inactivity, defined as not reaching global PA guidelines, causes 6% of the global CVD burden and has overtaken smoking as the primary cause of all-cause mortality (21).

Evidence from the past decade indicates that PA may not be the only mediator of health and development of noncommunicable diseases. Recent studies have provided evidence that sedentary behavior (SB: *i.e.*, sitting, lying) is associated with negative health connotations (8). More specifically, these studies report an association between prolonged periods of SB and all-cause morbidity and mortality, which cannot be simply explained by differences in engagement in low-, moderate- or vigorous-intensity PA (5). Similarly, studies have demonstrated a comparable relationship between SB and development of metabolic disease (*e.g.*, obesity, metabolic syndrome, and type 2 diabetes mellitus). Consequently, SB has emerged as a critical mediator of health in its own right. As a result of advances in entertainment and transport technologies, as well as the increased reliance on workplace technology and office work, SB is now the predominant behavior for a large amount of the population in developed countries (28); SB is therefore a clinically relevant target when changing lifestyle behavior.

Previous work has predominantly focused on the relationship between SB and all-cause or CVD mortality and/or metabolic

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disorders. In this article however, we will focus on the relationship between SB and the development of CVD. More specifically, we aim to synthesize, for the first time, scientific work that examines the relationship between SB and development of CVD and cardiovascular (CV) risk factors, and present an overview of studies that explore the mechanism(s) that underlie this relationship. To meet these aims, this article will i) assess whether the negative CV effects are borne from the removal of PA, ii) investigate the relationship between SB and CVD risk factors, iii) describe the effects of (acute and chronic) uninterrupted sitting on CV health, iv) discuss potential mechanisms that mediate the relationship between SB and CVD risk, and v) provide recommendations for future directions.

Is Sedentary Behavior Simply the Removal of Activity?

The Australian Diabetes, Obesity, and Lifestyle study (AusDiab), a population-based longitudinal study, examined the relationship between SB and CVD development with self-reported television (TV) viewing time as a surrogate marker for SB (8). The authors found that prolonged periods (≥4 h per day) of TV viewing time was associated with increased risk of CVD mortality, and each additional hour of viewing time was associated with an increased CVD mortality risk of 18%. However, because of limitations associated with correlation analysis and the confounding relationship between TV viewing and caloric intake, direct independent inferences could not be made. Subsequent studies, however, have provided additional insight into the association between SB and CVD, with a recent meta-analysis of 14 studies confirming that high SB was associated with increased CVD incidence (hazard ratio [HR], 1.143; confidence interval [CI], 1.002–1.729]) and mortality (HR, 1.179; CI, 1.106–1.257)(5).

One possible explanation for the associations between SB and CVD risk is that this relationship is merely due to a lack of PA rather than presence of SB. However, the evidence suggests the contrary, in that SB is related to CVD risk independent of engagement in low-, moderate- and/or vigorous-intensity exercise or physical activity (11). For example, in adults meeting weekly PA guidelines, dose–response associations are still observed between television viewing time and cardiometabolic risk factors (*e.g.*, waist circumference, systolic blood pressure (SBP), and 2-h plasma glucose) (12). Moreover, individuals participating in more than 7 $h \cdot wk^{-1}$ of moderate-to-vigorous PA, yet also accruing more than 7 h daily television watching, present a twofold greater risk of CV mortality compared with those engaging in 7 $h \cdot wk^{-1}$ of moderate-to-vigorous PA and only 1 h daily television viewing time (23). Furthermore, a recent systematic review and meta-analysis of studies assessing all forms of SB found that SB was independently associated with increased risk for CVD incidence and mortality regardless of PA (5). Nonetheless, the risk of mortality associated with sitting 10 $h \cdot d^{-1}$ may be modulated by PA as the risk for mortality in the sedentary group was 52% higher than those who sit for 1 $h \cdot d^{-1}$ but were inactive individuals, whereas this risk was reduced to 34% in active individuals (7). Therefore, these data suggest that the amount of SB is directly (and positively) related to development of CVD and largely independent from engagement in moderate-to-vigorous PA in the general population.

Is Sedentary Behavior Related to Cardiovascular Risk Factors?

The assertion of an independent relationship between SB and CVD mortality and morbidity raises the question of what mechanisms contribute to this observation. One potential, and somewhat obvious, explanation relates to the impact of SB on traditional CVD risk factors. In populations of healthy volunteers, studies have provided some evidence for a relationship between SB and traditional CV risk factors. For example, Stamatakis *et al.* (36) observed associations between SB and traditional CV risk (*e.g.*, body mass index [BMI], waist circumference, BP, high-density lipoprotein [HDL] cholesterol) in a population of 5948 healthy, middle-aged participants. In another cohort of healthy young adults (n = 2328), sitting time was positively and independently associated with resting heart rate and adiposity and was negatively associated with cardiorespiratory fitness (15). Generally, there is little scientific evidence in healthy populations that SB is related to total cholesterol or levels of low-density lipoproteins (6). However, studies have identified a positive association between SB and HDL and triglyceride levels in asymptomatic groups (2,6,35), which is largely independent of PA (2,35).

Relationships between SB and CV risk factors also are apparent in populations with CV risk and/or disease. For example, zmore time in SB is associated with higher BP ($r = 0.56$, $P < 0.01$) in hypertensive patients (9). In severely obese subjects, SB shows a positive, independent relationship with systolic BP, with every additional hour of sitting associated with a 14% higher risk of developing hypertension (17). Beunza *et al.* (4) followed up on these observations in a prospective, dynamic cohort study, which assessed the incidence of hypertension in 6742 healthy university graduates across a 40-month period. They found that the most sedentary subjects had a 48% increased risk of development of hypertension compared with their nonsedentary peers, (HR 1.48; 95% CI, 1.01–2.18; P for trend = 0.03) (4), an effect independent of PA levels. Although this area of research shows promise, there are very little data available; the role of SB in CV risk factor development in high-risk populations therefore warrants further investigation.

In addition to traditional CV risk factors, some recent studies have explored the possible relationship between SB and direct measures of artery health. This is relevant because modulation of traditional CV risk factors alone cannot explain the benefits of PA. The cardioprotective benefits of PA that cannot be explained through traditional risk factors, *i.e.*, the *risk factor gap*, may relate to the effects of PA directly on vascular health. Similarly, SB also may affect CV risk through direct effects on the vasculature (Fig. 1). In a cross-sectional analysis of 945 men, after adjusting for covariates (systolic BP and BMI), each additional 30 min of sedentary time was associated with an odds ratio of 1.19 (95% CI, 1.07–1.33) for a low ankle-brachial index (*i.e.*, <0.9) (30). In another cross-sectional study, it was observed that weekend SB was positively associated with arterial stiffness (men, $r = 0.11$, $P < 0.01$; women, $r = 0.08$, $P < 0.05$) even after adjustment for vigorous PA, resting heart rate, adiposity, and metabolic syndrome (15). In addition, in a healthy sample of 614 middle-aged adults, the ratio between sedentary time and time in light-intensity PA was positively associated with carotid intima media thickness ($r = 0.19$, $P < 0.05$) (18). Taken together, these data provide preliminary evidence that

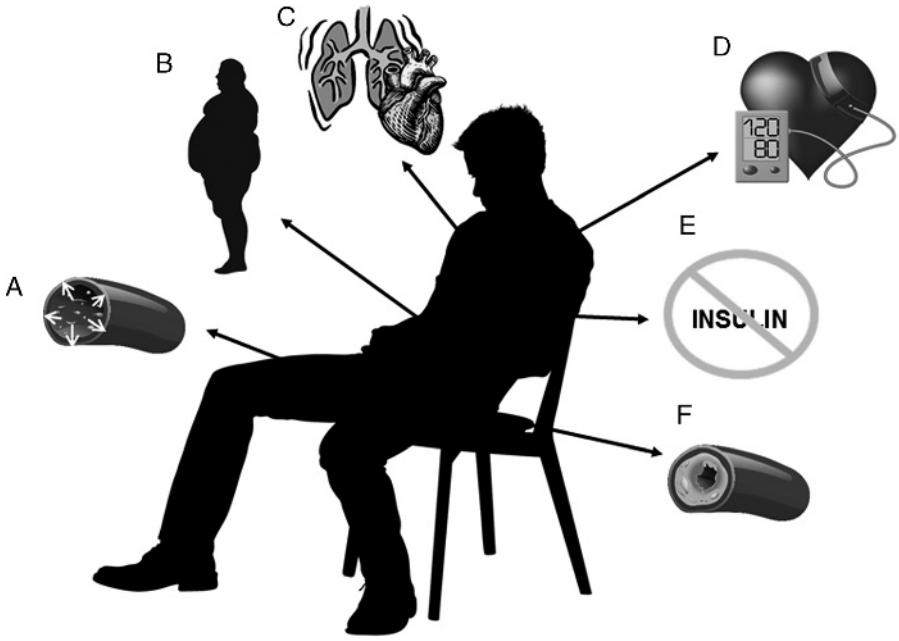

Figure 1. Schematic depicting the effect of sedentary behavior (SB) on cardiovascular disease (CVD) risk factors: A. Vascular structure and function: stiffness and intima-media thickness increase; endothelial function decreases. B. Body mass index increases. C. Cardiorespiratory fitness decreases. D. Blood pressure increases. E. Insulin resistance increases. F. Blood lipids increase.

SB is related to impaired vascular function and structure, although more work is required to truly understand this complex relationship and assess whether these effects are independent of CV risk factors. This is highly relevant because, together with the impact of SB on traditional risk factors, these effects may contribute to the increased risk for CVD associated with increased SB in both healthy as well as symptomatic populations.

Do Acute Periods of Sitting Impair Cardiovascular Health?

To better understand the long-term effect of sitting, recent research has explored the impact of short periods (3–6 h) of sitting on CV outcomes (Table). During a 3-h period of uninterrupted sitting, Padilla *et al.* (29) observed a significant increase in systolic and diastolic BP, evident after 1 h of sitting and accompanied by a simultaneous decline in popliteal blood flow and shear rate. More recently, Thosar *et al.* (37) observed a decrease in superficial femoral artery (SFA) endothelial function from baseline levels (baseline: 4.72% ± 3.78%, 1 h: 0.52% ± 0.85%, 2 h: 1.66% ± 1.11%, 3 h: 2.2% ± 2.15%; $P < 0.05$), and a concomitant reduction in antegrade and mean shear rate in response to a 3-h period of sitting. This work suggests that lower limb endothelial function is impaired after a period of uninterrupted sitting. In contrast, 3 h of uninterrupted sitting did not affect brachial artery (BA) endothelial function or mean shear. Importantly, upper limb movement was uncontrolled in this study, although previous work on lower limb conduit artery endothelial function and shear rate prevented lower limb movement. Restricting bodily movement therefore seems key for the downregulation of endothelial function, with even small movements being able to maintain blood flow and endothelial function (39).

TABLE. Summary of studies examining the cardiovascular effects of sitting interventions

First author	N	Follow-Up	Population	Intervention	Outcome Variable	Conclusion
Peddie (23)	70	9 h	Adults	1.40-min breaks every 30 min	Triglycerides, glucose, insulin	No difference in triglyceride levels between activity breaks and prolonged sitting
Bailey (24)	10	5 h	Adults	2-min breaks every 20 min	Blood pressure, lipids glucose	No difference in BP and lipid levels between activity breaks and prolonged sitting
Larsen (25)	19	3 d	Overweight	2-min breaks every 20 min	Triglycerides, glucose, insulin	No difference in triglyceride levels after 1 and 3 d between interrupted and uninterrupted sitting
Larsen (22)	19	7 h	Overweight	2-min breaks every 20 min	Blood pressure, heart rate	Lower SBP and DBP compared with prolonged sitting; no difference in mean arterial pressure or heart rate
Thosar (20)	12	3 h	Healthy men	5-min breaks every hour	SFA FMD, shear rate	Decline in FMD was prevented compared with prolonged sitting
Restaino (33)	10	3 h	Healthy men	Increased shear (using heat) during sitting	SFA FMD, shear rate	Impaired FMD during prolonged sitting was prevented by increasing shear
Morishima (27)	11	3 h	Healthy adults	1-min fidgeting breaks every 4 min.	SFA FMD	Fidgeting prevented a decline in shear rate and flow and improved FMD.
Graves (30)	47	8 wk	Adults	Sit-stand work station	BA FMD, BP, glucose, blood lipids	Improved cholesterol, possible benefits in blood pressure and FMD

BA indicates brachial artery; BP, blood pressure; DBP, diastolic BP; FMD, flow-mediated dilation used to assess endothelial function; SBP, systolic BP; SFA, superficial femoral artery.

The hypothesis that small amounts of movement prevent impairment in CV health associated with prolonged sitting has been explored in more detail in recent studies. Larsen *et al.* (20) observed significantly lower post-test systolic and diastolic BPs when 7 h of sitting were interrupted with self-selected, Borg Scale–determined, light- or moderate-intensity 2-min walking breaks every 20 min (SBP sitting: 123 ± 1 mm Hg, light: 120 ± 1 mm Hg, $P = 0.002$; moderate: 121 ± 1 mm Hg, $P = 0.02$; DBP: sitting: 79 ± 1 mm Hg, light: 76 ± 1 mm Hg, $P = 0.006$; moderate: 77 ± 1 mm Hg, $P = 0.03$). When data were stratified according to baseline BP, the largest effects of physical activity breaks on BP were found in those with increased BP *a priori*. These observations suggest that targeting SB may be especially relevant in those with higher CV risk. The impact of regular activity breaks from sitting has also been assessed on triglyceride and lipid levels (5 h–3 d). Perhaps unsurprisingly, given the duration normally required to alter these parameters, no effect of sitting was observed on triglycerides and lipids (3,19,31). Possibly, longer intervention periods are required to impact lipid parameters. Given the limited data on this topic, further research is warranted to better understand the acute effects of breaking up sitting using physical activity on CV risk factors.

The effects of prolonged, uninterrupted sitting and PA breaks also have been explored in relation to measures of endothelial function. In healthy, nonobese men, 5 min of light-intensity treadmill walking (2 miles·hr^{-1}) every 60 min prevented the decline in flow-mediated dilation and shear rate in SFA observed after 3 h of uninterrupted sitting (37). In line with these observations, others reported similar beneficial effects of regular activity breaks on SFA flow-mediated dilation in a cohort of healthy young girls (24). This study demonstrated that the reduction in SFA endothelial function associated with 3 h of prolonged sitting (mean difference, 2.2% flow-mediated dilatation; 95% CI = 0.60–2.94%, $P < 0.001$) was offset when participants undertook hourly moderate intensity cycling for 10 min. Together, these data support the hypothesis that regular PA breaks, which intermittently increase lower limb muscle activity level, prevent the decline in resting flow and endothelial function associated with prolonged, uninterrupted sitting. More recently, studies have had some success in preventing sitting-induced endothelial dysfunction using alternative physical activity interventions such as fidgeting (25), which was found to prevent the decline in blood flow and shear rate observed during prolonged, uninterrupted sitting. These data suggest that sitting-induced endothelial dysfunction can be offset via interventions that promote (low-intensity) physical activity.

Does Chronic Sitting Impair Cardiovascular Health?

To our knowledge, few studies have directly examined the consequences of longer term, acute exposure (>1 d) to SB on CV risk factors. Lyden *et al.* (22) investigated the effects of 7 d of increased sitting time and reduced breaks from sitting on lipids and markers of insulin resistance in 10 healthy young subjects. Compared with baseline, 7 d of SB caused no change in fasting plasma lipids, waist circumference, and BMI. Nonetheless, 2-h plasma insulin and area under the curve, as measured by oral glucose tolerance test, were significantly increased after the 7-d period of increased SB, indicative of the ability of SB to cause insulin resistance within 1 wk (22). Another study explored the impact of a 3-d intervention of either 7 h per day of uninterrupted sitting or 7 h of sitting with 2-min light-intensity walks every 20 min (19). Significantly lower glucose and insulin area under the curve, as measured by mixed-meal tolerance test, was found after only 3 d of uninterrupted sitting compared with the break condition. In line with previous findings, triglycerides did not differ between uninterrupted sitting and intervention. Therefore, studies on the immediate (3–6 h) and short-term (3–7 d) effects of SB suggest the presence of significant impairment in measures of insulin resistance, although no such changes were present in lipid levels.

A likely explanation for the absence of an effect of (short-term) SB on lipids may relate to the duration of the intervention. In line with work related to exercise training, longer term interventions may be required to alter lipid levels. Indeed, a study in which office workers reduced sitting time by 137 min over a 3-month intervention period showed positive effects on HDL cholesterol (1). Similarly, in a study by Graves *et al.* (10), self-selected use of standing work stations resulted in a mean reduction in sitting time of 90 min per day over an 8-wk intervention period. Consequently, a significant reduction in total cholesterol level was observed, supporting the idea that prolonged periods of physical (in)activity are required to alter lipid levels. In addition, this is the only study, to our knowledge, to have examined the endothelial response to long-term reductions in sitting time. Despite nonsignificant effects, the study also performed inferential statistics, which indicated "potentially clinically meaningful" improvements in BA endothelial function as well as "possible benefits" in the reduction in diastolic BP after the 8-wk intervention that reduced sitting time with ~90 min per day. In conclusion, short- and long-term periods of SB are able to alter peripheral blood flow and artery endothelial function as well BP. Future work is required to better understand these effects, especially because these impacts may differ between groups or between different interventions to alter SB.

What Are the Mechanism(s) Underlying SB-Induced Changes in Vascular Function?

Recent experimental evidence suggests that changes in CV risk factors, but also impairments to vascular health, likely contribute to the potentially detrimental effects of prolonged, uninterrupted SB on CVD (Fig. 2). Here, we will focus on understanding the mechanisms underlying the impairment in vascular health.

Hemodynamic stimuli

Previous work has revealed a central role for hemodynamic stimuli, such as shear stress, in mediating functional and structural changes in vascular health (16). Similarly, prolonged, uninterrupted sitting is associated with changes in shear that can mediate vascular dysfunction. Early work, which used prolonged sitting as a model to increase hydrostatic pressure on the lower limbs, observed that sitting for 3 h reduced mean, minimum and maximum shear rate in the popliteal artery (29). Indirect evidence for shear stress to mediate changes in endothelial function with SB is provided by Restaino *et al.* (32). They found that 3–4 h of sitting reduced blood flow and shear rate in lower limb conduit arteries, but not in the brachial arteries. These observations were associated with a decline in lower limb artery endothelial function, but not BA endothelial

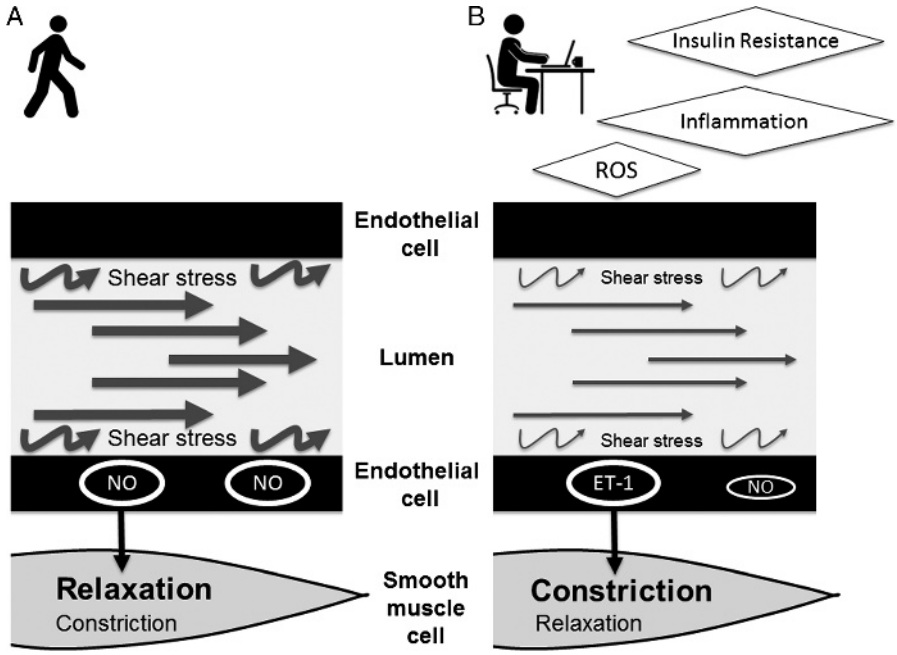

Figure 2. Summary of the potential mechanisms underlying sitting-induced cardiovascular disease risk. A. Represents an artery during walking, whereas (B) represents an artery after a period of sedentary behavior, whereby blood flow and shear stress are reduced, attenuating nitric oxide (NO) and increasing endothelin (ET-1) production, subsequently leading to vascular dysfunction. In addition, insulin resistance, inflammation, and reactive oxygen species (ROS) production may further augment this vascular dysfunction.

function. Another study examining lower and upper limb blood flow and endothelial function using an uninterrupted sitting period of 3 h (39) noted reductions in both popliteal and brachial shear, but only popliteal endothelial function. The BA may therefore exhibit greater resilience to shear rate reductions or longer periods are required to successfully affect perfusion and/or vascular health (32).

Although these observations provide some indirect evidence for the role of shear, more recent work directly explored the hypothesis that changes in shear mediate the decrease in endothelial function during prolonged, uninterrupted sitting. In healthy young men, popliteal artery endothelial dysfunction induced by 3 h of uninterrupted sitting was successfully attenuated by manipulating popliteal perfusion by local heating (33) or by small fidgeting leg movements (25). Both interventions successfully prevented the reduction in mean shear associated with prolonged, uninterrupted sitting. Consequently, both studies maintained or increased mean shear in the lower limbs from baseline levels, either through metabolic flow (*i.e.*, PA related [prefidgeting: $33.7 \pm 2.6\ s^{-1}$ to immediately postfidgeting: $222.7 \pm 28.3\ s^{-1}$; $P < 0.001$]) or non—metabolic flow (*i.e.*, induced by heat [presit, $38.9 \pm 3.4\ s^{-1}$; and 3-h sit, $63.9 \pm 16.9\ s^{-1}$; $P > 0.05$]), which successfully prevented the reduction in popliteal artery endothelial function.

In addition to reductions in mean shear rate, the patterns of shear may be equally important. Shear patterns have a key role in maintaining vascular function; antegrade shear stress preserves or enhances endothelial function by activating nitric oxide production; although low and oscillatory shear stress can promote atherosclerosis, inflammation, and increased oxidative stress (16). Antegrade shear is reduced in the SFA and BA during 3 h of uninterrupted sitting, although oscillatory shear is increased in the BA (39). Interestingly, changes in the shear pattern of both vessels occurred over distinct time courses. The reduction in femoral artery antegrade shear was evident after only 1 h of sitting, which coincided with the reduction in SFA endothelial function. In contrast, however, changes in BA antegrade and oscillatory shear were observed after 3 h of uninterrupted sitting. These data indicate that over a relatively short time scale (1 h), uninterrupted sitting elicits negative effects on antegrade and oscillatory shear and, consequently, endothelial function in the lower limbs. However, the negative SB effects on shear patterns in the upper limb occur over a longer period (3 h) and are not accompanied by endothelial reductions (39). Studies of a longer duration are needed to fully examine the effects of sitting-induced alterations in shear pattern on endothelial function.

The underlying mechanisms that contribute to the changes in shear are currently unknown. One potential mechanism may relate to the exposure to prolonged gravitational forces, which may increase hydrostatic pressure within the lower limbs, causing venous pooling and subsequent reductions in blood flow and shear stress (32). Prolonged sitting leads to increased calf circumference (32), calf pooling, and decreased thigh blood flow (40). In addition, increased muscle sympathetic nerve activity and changes in blood viscosity also may contribute to altered shear rates and endothelial dysfunction (32). Insight into the pathways that underlie the dysfunctional vascular environment in response to sitting also is limited. Previous work provides strong evidence that lower shear rates decrease nitric oxide availability and increase production of vasoconstrictors such as endothelin-1, although lower shear rate also is conducive to the expression of atherogenic genes and inhibition of antiatherogenic genes (40). Compared with standing, sitting elicits changes in the angles of the major arteries, which may increase turbulent flow and shear patterns known to augment the

atherosclerotic process (40). These factors may all, in part, contribute to the strong link between prolonged, uninterrupted sitting and impaired vascular health.

Inflammation and reactive oxygen species

There is a strong association between elevated inflammatory markers and impaired vascular function. Inflammatory markers also are associated with reduced nitric oxide availability, CVD incidence, and risk prediction (13,41). Previous work found that higher self-reported sitting is associated with higher levels of adipokines and low-grade inflammation, an observation that was independent of PA levels (14). Cross-sectional and prospective studies also have shown that longer sitting time is associated with higher levels of C-reactive protein, a marker of systemic inflammation (13,14). However, this association between C-reactive protein and SB was attenuated or lost after controlling for BMI or waist circumference, suggesting that adiposity levels may mediate this relationship (13,14). Despite the presence of some observational evidence that sitting is associated with the presence of markers of (low grade) inflammation, no study has directly examined the impact of SB on these markers and/or linked these changes in markers of inflammation to changes in endothelial function.

Inflammatory cytokines also activate vascular production of reactive oxygen species (ROS) (41), which may further explain the association between SB and CVD risk. Production of ROS is regarded as an important component in the pathogenesis of CVD, particularly because of the production of superoxide, which is associated with impairments to endothelial function and hypertension (41). Interestingly, a recent study examined whether the reduction in SFA endothelial function after 3 h of uninterrupted sitting could be prevented by oral administration of vitamin C, a potent ROS scavenger (38). Although the sitting-induced reduction in SFA endothelial function was successfully prevented by intake of vitamin C, this study did not perform additional testing to confirm that vitamin C was indeed responsible for a reduction in oxidative stress. These initial findings support further work to focus on a potential role for ROS to contribute to the impact of prolonged sitting on vascular health.

Metabolic markers

The link between SB and metabolic health has been well documented, with experimental research demonstrating detrimental changes in blood insulin and glucose levels as a result of prolonged, uninterrupted sitting. Insulin resistance is associated with endothelial dysfunction because of an imbalance between the phosphatidylinositol 3-kinase (PI3K)–dependent and mitogen-activated protein kinase (MAPK)–dependent signaling pathways (27). In an insulin-resistant state, PI3K signaling is reduced leading to decreased nitric oxide availability, although MAPK signaling is unaffected, leading to greater endothlin-1 production, endothelial cell apoptosis, and inflammation (27). Furthermore, sedentary time results in longer periods of postprandial hyperglycemia (27), which may have a mechanistic contribution because acute and prolonged periods of hyperglycemia also are known to impair endothelial function. The effects of hyperglycemia occur via several mechanism including increased ROS production, increased advanced glycation end-products formation, and the activation of protein kinase C, which ultimately results in heightened oxidative stress, apoptosis, and increased vascular permeability (34). Therefore, the detrimental effect of sitting on CV health may, at least in part, be the result of metabolic dysfunction and its subsequent effects on the vasculature.

Conclusion and Future Directions

A significant body of evidence indicates that prolonged sitting is associated with increased risk for developing CVD, and that this association between SB and CVD cannot be explained simply by the absence of moderate-to-vigorous PA. Research provides strong evidence that this link is, at least partially, due to sitting-induced alterations to traditional CV risk factors, including glucose tolerance, BP, and lipid profile (via HDL), as well as impairment in vascular health mediated by reductions in mean and antegrade blood flow and shear rate. Recent work also highlights a potential role for increased ROS production, presence of low-grade inflammation, and metabolic impairment to contribute to sitting-induced impaired vascular function. However, this field is in its infancy, and several important questions need to be answered to better understand the impact of SB on CV health.

Laboratory studies indicate that regularly interrupting sitting seems to be more important than the total duration of sitting to prevent the effects on the CV system; however, epidemiological evidence for this is currently lacking. Furthermore, relatively little is known, both from epidemiological and (pre)clinical work, whether the impact of targeting SB is equally relevant in healthy, physically active subjects versus physically inactive subjects with or without CV disease and/or risk. Better understanding in this area would highlight which population would potentially benefit most. To further understand potential mechanisms underlying sitting-induced vascular dysfunction and increased CVD risk, studies should explore blood-borne markers such as circulating endothelial progenitor cells and whether (long term) SB may contribute to changes in measures of vascular structure. Furthermore, research has focused largely on the influence of SB on conduit arteries, other vascular beds including the coronary, peripheral resistance and cerebrovascular beds should be explored.

To date, the direct influence of SB on CVD (risk factors) has been studied only after a short period of altered SB. This highlights the need for well-designed and properly powered studies that examine the impact of longer term follow-up on both the impact of SB, as well as interventions that counteract these detrimental effects. This work is required to better understand the impact of SB, to enhance the ecological value of research in this area, and importantly to develop specific public health guidelines for daily sitting time.

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