Sitting Less *and* Moving More: Implications for Hypertension

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Introduction

On the basis of recent changes to blood pressure (BP) guidelines[1], some 46% of Americans (a further 31 million people) are now classified as having hypertension (BP ≥130/80 mmHg). This new classification recognizes the recent clinical trial evidence regarding the benefits of lower BP targets[2] and, among other factors, emphasizes the importance of considering how non-pharmacological strategies (i.e., lifestyle modification) can be better incorporated into broader prevention messages[3]. In this context, and with conventional guidelines focusing on moderate-vigorous physical activity, there is unrealized potential for benefitting a large proportion of the at-risk population through broadening the range of physical activity options in ways that might be more amenable to lifetime adherence.

Although the benefits of a physically active lifestyle for overall cardiometabolic health – including BP control – are well known[4-7], a large and growing proportion of the global population are physically inactive[8, 9]. Worksites, schools, homes and public spaces are physically engineered and socially arranged in ways that *minimize regular movement* and muscular activity, and *maximize the time spent sitting*. This is against a background of unprecedented demographic shifts associated with the aging of populations, with higher proportions experiencing more years of frailty, a range of chronic non-communicable diseases and risk factors, and poorer physical function and quality of life. Aside from contributing significantly to increases in healthcare costs, these combined factors represent a formidable set of clinical and public health challenges.

The contribution of low rates of participation in moderate-vigorous physical activity to the chronic disease burden has provided the impetus to explore the efficacy of physical activity options which are more amenable to lifetime adherence and that have broader population reach. In this regard, emerging strategies focusing on reducing and changing the patterns of

sedentary behaviors (put simply, *too much sitting*) may have potential for lowering the incidence and prevalence of hypertension, as well as minimizing medication use in those already treated.

Through a hypertension lens, this review focuses on the potential health implications and some of the plausible counter-measures for the high volumes of prolonged sitting that now characterize modern lifestyles. We synthesize findings on the specific relationships of sedentary behavior with BP – which primarily are from observational and acute experimental studies – including a discussion on the relevant cardiovascular mechanisms. We also consider what will need to be better understood as a basis for evidence-based recommendations on sedentary time in the context of BP control, and identify evidence gaps for future research.

Sedentary Behavior: a Newly-Identified Element for Chronic Disease Risk and a Target for Management

Regular moderate-vigorous physical activity is well-established as an effective tool in the prevention and management of multiple chronic diseases, including hypertension[4, 7]. However, in recent years, sedentary behavior – defined as "any waking behavior characterized by an energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting or reclining posture" – has received increasing attention as a clinical and population health problem that is *additional to* insufficient moderate-vigorous physical activity[10]. Reasons for this new perspective around sedentary behavior largely stem from three key points (expanded upon below). For clarity and distinction, we refer to recommended amounts of moderate-to-vigorous intensity physical activity as ''exercise'' and use the terms "sitting" and "sedentary behavior" interchangeably throughout this paper[7].

1) *Modest uptake and adherence to exercise guidelines*: Despite the multitude of potential health benefits derived from regular physical activity, population uptake is low. One-third of many adult populations (about 1.5 billion people globally) and four-fifths of adolescents do not adhere to minimum recommended levels of moderate-vigorous physical activity[8]. While leisure-related physical activity levels have tended to remain relatively steady over time, physical activity at work, in the domestic environment and in transportation have all decreased in recent decades[8, 9]. Sustained and growing concerns also exist around the limited uptake and adherence to exercise guidelines in longer-term trials[11] and in accordance with national/global activity guidelines, particularly for older adults and in deconditioned/clinical populations[8, 12-15].

2) *High volume of waking hours spent sedentary*: In developed countries, and in the rapidly urbanizing populations of developing countries, sedentary behaviors have become the primary default behavioral option – inextricably embedded in work, school, transport, and leisure-time. Data obtained from studies using accelerometers, mainly from America and Australia, indicates that adults spend on average 55–70% of their waking hours (or over 8-10 hours/day) engaged in sedentary behaviors[16-18]. Furthermore, recent Australian-based data (*AusDiab3*) suggests that just under half of the ~9 hours of total *sitting* time (as measured by posture-sensitive accelerometers)[19] is spent in prolonged unbroken bouts of greater than 30 minutes, and that just over half of all adults accumulated more than 4 hours per day of their sitting time in this manner (Figure 1).

3) *Evidence on the associations of total sedentary time, and its pattern of accumulation, with cardiometabolic risk:* Prospective epidemiological evidence suggests that high volumes of sedentary time are associated with premature mortality and cardiometabolic risk biomarkers for type 2 diabetes, cardiovascular disease, and certain cancers. These deleterious

associations are partly moderated by time spent in moderate-vigorous physical activity, but are particularly evident in those who undertake insufficient or no moderate-vigorous physical activity[7, 20, 21]. Furthermore, accumulating observational and experimental evidence indicates that specific patterns of sedentary time (i.e., whether sitting is undertaken in prolonged or regular intermittent bouts) may be differentially associated with a number of cardiometabolic risk biomarkers and premature mortality[19, 22-25]. For example, a recent large-scale observational study found that both total sedentary time and prolonged uninterrupted sedentary bouts were associated with an increased risk for all-cause mortality, after controlling for moderate-vigorous physical activity and traditional cardiovascular risk factors[24]. Another recent cross-sectional study, using inclinometer data from a subset of *AusDiab3* participants (also see Figure 1 from the same cohort), showed that both greater amounts of sitting time and prolonged sitting time were deleteriously associated with waist circumference, BMI, HDL-cholesterol, triglycerides, 2-hour post-load glucose, and fasting plasma glucose[23].

As a result, leading health agencies such as the American Heart Association[26] and the American Diabetes Association[27] have begun to acknowledge the likely clinical and population health impact of changing sedentary behaviors. Consideration of the mechanistic linkages of reducing and breaking up prolonged sitting with BP control and hypertension is highly relevant in this context. Indeed, evidence from epidemiologic observational studies and a new body of findings from acute experimental trials can provide helpful insights.

Sedentary Behavior and BP Control

Measurement challenges

There are significant challenges in objective quantification of both physical activity patterns and blood pressure, which make relational investigations difficult[28, 29]. Most observational

studies examining associations of sedentary behavior with BP and hypertension have typically relied on self-reported daily sitting or television/screen viewing time – methods that are susceptible to recall and response bias, social desirability, and under- or over-reporting[28]. Accelerometer-derived measures of movement and posture have been employed more recently to more "objectively" characterize sedentary and active behaviors, as they are less subject to the biases that are inherent to self-report. However, they are not without limitations. For example, these newer methods cannot determine the behavioral contexts (i.e., the location and purpose of these behaviors) and results may be influenced by wear-time differences, some activity misclassification (depending on device type/location), and data analysis approaches.

Particularly under conditions of normal daily living, BP measurement is associated with additional challenges. BP is an inherently labile parameter, with considerable temporal variation from heart beat to heart beat and across the 24-hour day. Thus, interpretation of a single time-of-day BP must be in a behavioral context which considers additional factors, such as dietary and fluid intake, physical activity, emotions, stress and drugs (including caffeine and nicotine). In addition, BP measurements can be dramatically affected by the "white coat" or "masked" effects in clinic/office settings, and is often measured under a variety of conditions (e.g., postures) with differing preceding rest periods. Although not without limitations, 24-hour ambulatory BP has better prognostic value than single office BP measurements, and is thus considered the reference standard to diagnose hypertension according to certain groups[29].

The above measurement challenges likely contribute to variability in observational evidence on the associations of sedentary behavior with BP and hypertension (almost always assessed

via resting office BP). Indeed, such evidence to date has been quite heterogeneous and inconsistent[30-34], with relatively small mean effect sizes.

Observational evidence

In a recent systematic review and meta-analysis, Lee and Wong[35] examined the associations of time spent in sedentary behaviors with BP in both adults and children. Of the 28 studies included in the meta-analysis (8 longitudinal, 20 cross-sectional), 10 assessed sedentary behavior via accelerometry and the remainder used self-report measures (i.e., television/screen viewing time, sitting time, or both). Results from this meta-analysis revealed that for each hour increase in *self-reported* sedentary behavior there was an associated small increase in systolic and diastolic BP of 0.06 (95% CI: 0.01-0.11) and 0.20 (0.10-0.29) mmHg, respectively. Additionally, for each hour increase in sedentary behavior there was a 2% elevation in risk for hypertension (OR=1.02, 95% CI: 1.003–1.03).

Interestingly, no significant associations were observed when sedentary time was assessed via accelerometry, although systolic BP was borderline significant at 0.10 (95% CI: -0.001 to 0.21, p=0.06) mmHg[35]. These discrepancies between the self-report and device-based exposure measures suggest either differences in measurement variability, validity and reliability (for both the sedentary behavior and the resting BP measures), poorer compliance with the use of the accelerometers (which has been shown to be lower in those with hypertension[36]), or that the disparity in timing of office BP measurements in relation to the active/sedentary behaviors and other factors (as mentioned previously) may also be important.

In one of the few observational studies to utilize both 7-day accelerometry and ambulatory BP measures, Hamer *et al*.,[37] showed, in a sample of 216 middle-aged Black- and Caucasian-

African school teachers with or at high risk of hypertension, that the positive associations of sedentary time with 24-hour BP (but not daytime or resting office BP) were primarily driven by the night-time readings. Further analyses showed that participants in the highest sedentary tertile were also more likely to be night-time 'non-dippers' (OR=2.11, 95% CI: 0.99–4.46, p=0.052) compared with those in the lowest sedentary tertile. These night-time specific BP findings for the more sedentary participants are intriguing, since ambulatory BP-derived sleep BP (presence/absence of dipping) tends to be a more stable BP measure, and is a stronger predictor of cardiovascular risk, independent of office BP or wake-time BP[38]. The findings could be due to elevated night-time sympathetic activation, which is consistent with the findings from one experimental study demonstrating higher plasma noradrenaline levels during prolonged sitting[39]. Alternatively, BP readings are generally more stable nocturnally. However, there is also the potential for measurement issues, since study participants were required to sleep in unfamiliar surroundings at the overnight clinical facility. Importantly, the study also showed that those who spent less daily time in light-intensity physical activity (the corollary of spending more time sedentary) had significantly higher 24 h ambulatory and daytime systolic and diastolic BP, as well as higher resting systolic BP.

It is thus difficult to draw any firm conclusions from the observational evidence to date. The question of whether sedentary behavior is an acute BP "stressor", as distinct from other conventional risk factors which contribute to sustained BP elevation (e.g., age, obesity, diabetes), is difficult to disentangle. Ambulatory BP measures may be better suited for studying the patterning of BP on days characterized by periods of prolonged sitting. Thus further prospective study evidence using ambulatory BP methods, and with more detailed sensor-assessed measures of sitting patterns *per se* and their context, would be highly informative. Consideration of the specific population (e.g., normotensive and uncomplicated hypertension, medication) in these contexts will also be important.

Experimental evidence

Few studies have examined the effects of prolonged sitting on BP (see Supplementary Table S1 for a summary of the relevant acute studies published to date). Most studies[39-45], but not all[46, 47], have observed significant systolic or diastolic BP-lowering effects when prolonged sitting time has been reduced or interrupted (mostly with walking breaks, but also some with standing breaks), ranging from 1 to 16 mmHg in magnitude. However, the majority of studies have generally included BP as a secondary endpoint, which may limit the rigor and interpretability of the BP findings.

Although not an entirely consistent phenomenon, reductions in BP with activity-breaks in prolonged sitting have tended to be more modest in the physically active healthy-younger populations, but most pronounced in older, 'at-risk' populations and/or those with overt or pre-hypertension. For example, in inactive overweight/obese adults (over half of which were classed as having pre- hypertension or hypertension), interrupting sitting time with brief bouts of either light- or moderate-intensity walking significantly lowered resting systolic and diastolic BP by ~2–3 mmHg[43]. Similarly, reductions in resting systolic and diastolic BP of significantly greater magnitude (mean ↓14-16 and ↓8-10 mmHg respectively) were shown when sitting was interrupted with either light-intensity walking or with simple resistance activities in adults with type 2 diabetes (of which 88% were also hypertensive)[39]. These latter two laboratory-based studies support the contention that the magnitude of BP-lowering by interrupting sitting time, or the BP-increase with prolonged uninterrupted sitting, may be greater in hypertensive compared to normotensive groups. Moreover, BP-reductions in these two studies were established on top of standard antihypertensive medications.

To further explore the hypothesis that those with hypertension may be more susceptible to BP elevation with prolonged sitting exposures, and/or derive more benefit from reducing and breaking up sitting time, we pooled data from four separate laboratory-based randomized cross-over trials. These studies examined the BP responses to prolonged uninterrupted sitting versus sitting interrupted by regular 2-3 minute walking breaks (Figure 2A) or by regular 3 minute simple resistance activity breaks (half-squats, calf raises, gluteal contractions and knee raises; Figure 2B) in overweight/obese adults with and without hypertension. Figure 2 and accompanying Supplementary Table S2 illustrate two key points:

(1) that prolonged uninterrupted sitting appears to evoke increases in both systolic and diastolic BP in a manner proportional to the length of time spent sitting, and that the magnitude of these changes are generally greater and more clinically relevant in those with hypertension compared to normotensives;

(2) and, that regular breaks in prolonged sitting with either light-walking breaks or simple resistance activity breaks reduces both systolic and diastolic BP by a greater magnitude for simple resistance activity breaks in both normotensive and hypertensive populations.

The simple resistance activity breaks that have been employed in these recent trials were designed to provide an alternative option to walking breaks, which usually obliges a person to leave their immediate location. They require no specialized equipment and only small amounts of floor space. In addition, the compound/multi-joint nature of these activities engages a significant muscle mass in contractile activity, and when performed regularly, could increase functional capacity and insulin sensitivity through maintenance or increases in muscle mass and adaptations in metabolic enzymes. These factors may be particularly relevant for overweight and ageing populations with hypertension[48], the vast majority of

whom do not engage in sufficient moderate-vigorous nor muscle-strengthening activities, in accordance with national activity guidelines[7, 49]. If these findings are corroborated by further studies and in a chronic context, there are potential implications for future targeting and optimization of physical activity/sedentary behavior interventions in these populations groups.

Recent studies have also started to include more detailed ambulatory BP measures over consecutive days and while simulating "free-living" scenarios, which is providing insight into the sustained effects of sitting-reduction interventions. For example, Zeigler *et al*., showed that pre-hypertensive, overweight/obese adults accumulating 2.5 h of standing or light-intensity physical activity across the day equally reduced systolic and diastolic ambulatory BP both during and after working hours by ~3–4 mmHg[45] and ~2-13 mmHg[44] respectively, compared to a simulated 8 hour seated workday. Using a comparable design and measures, Bhammer *et al*.,[41] also showed similar reductions in systolic, diastolic and mean arterial BP (~5-6 mmHg) with moderate-, but not vigorous-intensity walking breaks, but these effects were only observed in the evening after the intervention period (outside of the laboratory).

The accumulation of the experimental findings described above are congruent with previous literature regarding the equally beneficial impact of fractionized vs. continuous exercise bouts[50-54], and the potential for a light-intensity physical activity 'threshold' for BP lowering[55, 56], which may even be related to simple postural changes (i.e., sit-to-stand transitions) across the day. Further prospective and longer-duration intervention studies of this nature, in more free-living settings and with ambulatory BP measures, will be important in elucidating whether prolonged sitting *per se* induces BP elevation. They will also assist in determining the efficacy and specificity of interventions that reduce and break up prolonged sitting time using a range of light-to-moderate intensity activities.

Teasing apart the impact of other confounding and interacting factors of everyday living, such as dietary, stress and sleep patterns, will continue to be a challenge – and may require more tailored study designs and advanced measurement and analytical approaches. The timing of BP measurements relative to activity and dietary factors will also be important, with a combination of parallel ambulatory BP measurements to determine BP reactivity in real-time, and well-standardized resting and ambulatory BP measures taken after the intervention period, in order to determine chronic BP changes.

Potential Physiological Mechanisms

Theoretical considerations

The potential underlying biological mechanisms by which a bout of prolonged sitting may acutely modulate BP are multiple, but ultimately must result from alterations in cardiac output and/or total peripheral resistance. In this context, mechanisms are likely to predominantly affect total peripheral resistance, and to include metabolic, autonomic and direct vascular mechanisms (Figure 3).

The concept that metabolism controls blood flow and thus drives pressure is a potentially important consideration with respect to understanding how prolonged sitting might modulate BP. Prolonged sitting is characterized by low energy expenditure or metabolic demand, as measured by indirect[57, 58] and whole-room calorimetry[59], where the average energy cost of common sedentary behaviors (reclining, watching television, reading, and typing on a computer) are narrowly banded around ~1.0 MET, even in the postprandial state[59]. Metabolic demand is the key determinant of blood flow in all tissues, with multiple mechanisms linking the metabolic requirements of tissues in terms of oxygen and substrates (glucose and fatty acids), to blood supply.

As described above, metabolic demand is low during prolonged sitting. Consequently, vasodilatory metabolites, including adenosine, are correspondingly low and the caliber of capillaries is therefore minimized. It would be expected that low metabolic demand would result in closure of precapillary sphincters and the shutdown of nutritive capillary beds (Figure 4). Capillary closure as a result of low metabolic demand within muscles reduces the pressure differential with upstream feed arteries, thus reducing blood flow via simple hemodynamics. As a consequence, vascular shear stress is reduced, promoting vasoconstriction through associated endothelial mediators (i.e., reduced nitric oxide and increased endothelin-1). Low metabolic demand therefore has the potential to increase peripheral resistance and drive BP up through effects at multiple levels of the vascular tree. A seated posture creates bends and constrictions in major blood vessels of the lower limbs, particularly under the thighs[60]. Such effects may result in simple mechanical increases in peripheral resistance, but also promote turbulent blood flow patterns, which may have acute and chronic consequences for blood flow and pressure regulation[61, 62].

A further consideration is that increased hydrostatic pressure and reduced venous return (i.e. via insufficient calf muscle pump activity) while seated also leads to fluid accumulation in the lower limbs that is proportional to the time spent sitting[63-65]. This fluid accumulation during the day likely shifts rostral overnight and is hypothesized to predispose or exacerbate obstructive sleep apnea – particularly in those with congestive heart failure or at increased risk for obstructive apnea[66-68] – which has been associated with nocturnal hypertension and non-dipping BP patterns[67]. Significant peripheral edema may also have implications for night-time BP elevation via carotid baroreceptor unloading (due to increased interstitial pressure), reduced baroreceptor afferent activity, and therefore a reflex increase in efferent

sympathetic activity – but these mechanistic links remain untested in the context of prolonged sitting.

Over time, habitual physical inactivity and high volumes of prolonged sitting are likely to result in weight gain, muscle atrophy, vascular rarefaction (reducing vascular volume), endothelial damage and stiffening of large arteries, potentially contributing to sustained elevation in peripheral resistance and hypertension. In this context, controlled chronic studies are required, in order to better understand any such longer-term structural and functional changes.

Given that prolonged sitting occurs over hours, concurrent behaviors are integral to the consideration of mechanistic influences on BP. Foremost among these is food intake, which will induce a higher nutrient load in the context of prolonged sitting, where muscular activity and hence energy expenditure are relatively low. The exaggerated elevations in circulating glucose and insulin levels documented to occur with prolonged sitting in association with feeding would be expected to cause sympathoexcitation and noradrenaline release from arterial nerve terminals. This represents another plausible pathway which may contribute to BP elevation during a bout of prolonged sitting.

A final issue to consider is that physical activity-induced muscle contraction, whether through multiple breaks in sitting or via a continuous bout, will have opposing effects on mechanisms associated with prolonged sitting by promoting energy metabolism and vasodilation.

The autonomic effects of brief activity bouts are more complex. While systolic BP, in particular, increases acutely during the performance of an activity (predominantly due to

resting BP between a day of prolonged sitting and a day of prolonged sitting interrupted by brief activity bouts may be related to:

(1) increases in BP from baseline mediated by prolonged sitting, and

(2) decreases in BP from baseline mediated by activity bouts.

While the physiological basis of the proposed mechanisms described above is sound, their validity requires testing in controlled laboratory studies which consider real-world behaviors, including food intake and stress that are present in different contexts (e.g., at work, during transportation, in leisure time).

Evidence

As noted earlier, the body of evidence on the mechanisms by which prolonged sitting may impact BP is in its infancy. While there are significant challenges to understanding the chronic BP effects in this context, acute physiological studies are providing some evidence to support the theoretical concepts discussed above. A number of studies have convincingly documented a prolonged sitting-induced increase in accumulation of extra-vascular fluid in the legs[63, 65-68] and a decline in leg flow-mediated dilation and/or shear stress measured in the superficial femoral[70-73] and popliteal[74, 75] arteries. These effects can be mitigated by various interventions promoting increased metabolic demand, muscle pump activity, and/or vasodilation, including frequent short low-intensity activity breaks[72, 73], static standing[74], fidgeting[70], calf/lower leg exercises while sitting[68, 76], bouts of cycling[74] or walking[71] and heating[75].

Direct measurement of vasoactive mediators (neurotransmitters and endothelium-derived factors) is challenging, since blood levels do not accurately reflect the physiologically relevant concentrations within the vasculature, and because some (e.g., nitric oxide) have very short half-lives. There is however some evidence for elevation in vasoconstrictor mediators in response to prolonged sitting. In patients with type 2 diabetes, Dempsey *et al*., observed an 11-18% increase in circulating noradrenaline in association with BP elevations of 10/5 mmHg during prolonged sitting[39]. These effects were mitigated by a magnitude similar to that typically achieved with pharmacological treatments if sustained[77], by interrupting prolonged sitting with brief bouts of light-intensity walking or simple resistance activities. It is also interesting that these effects were present even though 67% of participants in this study were medicated for hypertension and took their medications on the experimental days.

The expected downstream effects of sympathetic activation, including on the renin-angiotensin-aldosterone system, are yet to be studied in the context of prolonged sitting. Vasoactive endothelium-derived mediators are also likely important in the context of prolonged sitting exposures (see Figures 3 and 4), but evidence on these and other such mechanistic candidates is currently lacking. As previously mentioned, downregulation of nitric oxide due to shear stress reductions is probable. In addition, there is consistent evidence that prolonged sitting increases insulin resistance relative to regular activity breaks, particularly in those who have type 2 diabetes[25]. Insulin resistant states are associated with marked impairments in insulin-mediated vasodilatation and capillary perfusion of skeletal muscle, through endothelial mechanisms involving impaired nitric oxide bioavailability[78] and endothelin-1 upregulation[79-81]. Indeed, a recent study in overweight/obese adults showed that endothelin-1 levels are higher during a bout of prolonged sitting compared with sitting interrupted every 30 minutes by three minutes of simple resistance activities; however,

prolonged sitting *per se* did not elevate endothelin-1[73]. Insulin may also promote the expression of pro-atherogenic mediators including the intracellular adhesion and vascular cell adhesion molecules[82]. Taken together, it could be speculated that prolonged sitting-induced shear stress reduction, combined with impairments in lower limb arterial function and dilation[71, 72, 83] and the above CVD risk factors, may promote a pro-atherogenic environment. However, further investigations are required in order to elucidate the specific vascular mechanisms relevant to prolonged sitting, and its interruption by short activity breaks.

Mechanisms – summary

Preliminary evidence suggests that the BP-relevant effects of prolonged sitting include reduction in conduit vessel flow and elevation in vasoactive mediators. Theoretical considerations indicate that these effects are likely driven by metabolic demand and capillary caliber, but studies to date have not extended to the microvessels. The mechanisms contributing to the effects of habitual prolonged sitting on BP over an extended (chronic) period are indeterminate and will be challenging to investigate. Current knowledge of the cellular and molecular mediators of vascular pathophysiology would implicate chronic low grade inflammation and oxidative stress, as well as structural effects promoting vascular stiffening[84] as intermediaries between acute hemodynamic changes and manifestations of clinical hypertension (Figure 3).

Summary and Future Directions

Through a hypertension lens, we have highlighted potential new clinical and population health implications of sedentary behavior; also synthesizing the available evidence on prolonged sitting with respect to BP control. In this context, we have discussed the plausible mechanisms and the associated emerging evidence. While there are notable gaps in the currently available research literature on sedentary behavior and BP, accumulating

experimental evidence points to the potential importance of reducing and breaking up prolonged sitting for BP control, particularly in those who are more 'at risk', pre-hypertensive or hypertensive.

These findings reemphasize the major role that all aspects along the human movement continuum – from sedentary behavior through to moderate-vigorous physical activity – can play in influencing overall health and cardiovascular function. Initial evidence also hints that prolonged sitting *per se* may exert both direct and indirect effects on BP; however, much still remains to be understood and clarified. This area of research may be particularly important in the context of the recently revised US guidelines for the diagnosis, treatment, and management of hypertension[2], which now recognize the vital importance of incorporating lifestyle approaches into broader clinical and population health messages. In this context, we can offer some new directions for future research:

Longer-term exposures and interventions: There remains an urgent need for more chronic experimental trials and intervention-study evidence from real-world settings such as clinics and workplaces – with high quality BP measures as primary outcomes, sufficient controls, and adequate sample sizes/statistical power to detect changes. Such evidence will be required to determine the composition of sitting-reduction interventions that will have the largest impact on BP control and hypertension risk, and whether BP changes can be sustained over longer periods. This would also contribute to the elucidation of potential mechanisms by which both acute and longer-term interventions interrupting prolonged sitting may reduce BP.

More advanced measurement tools and analytic methods: To fully understand the inter-relationships between sedentary behavior, physical activity and BP, it is crucial to have high-quality and accurate measures of both the exposure and the outcome. The integration of data

from devices that are able to accurately assess both posture and activity patterns/intensities in real-time, alongside both office and ambulatory BP measures, should be emphasized in future research. Additionally, analytical techniques such as isotemporal substitution modelling and compositional data analysis will allow researchers to better account for the inevitable interdependencies and interactions between sedentary behaviors, physically active behaviors and sleep across the 24-hour day.

Identifying the optimal doses, patterning and timing of sedentary behaviors: Although there is acute evidence that reducing and breaking up prolonged sitting time with a range of light-moderate intensity activities may be beneficial for BP control, much less is known about the specific dose-related and patterning effects of these behaviors. The 'ideal' balance between sedentary behavior and physical activity for BP control is yet to be defined. Questions still remain around the optimal durations and thresholds of prolonged sitting time for BP control, and *what* range of postural or activity perturbations from sitting (i.e., frequency, type/mode, duration, timing and intensity) can produce the most benefit. These questions are inevitably complex, as the "ideal" patterning of sedentary and physical activity behaviors is likely to be based on the requirements, context, and activity/health status of the subpopulation, rather than a "one size fits all" approach. As such, more in-depth examination of the behavioral targets and feasibility to change in different populations will be informative in optimizing future intervention efforts.

Mechanisms, contexts and interacting effects: Evidence on the relative and/or integrated importance of the physiological states considered earlier in mediating the potential detrimental effects of prolonged sitting remains limited. Identifying the relevant mechanisms associated with prolonged sitting exposures, along with their relevant contexts and settings (e.g., workplace, leisure, transportation, TV/screen time), will be important in providing an

informed basis for clinical guidelines and public health targets. With this in mind, the impact on BP of reducing and breaking up prolonged sitting may interact with specific phenotypes, including but not limited to: gender, menopausal status, adiposity, age, ethnicity, genetic profiles, sleep, dietary habits, smoking, alcohol intake, medications, current cardiorespiratory fitness and baseline physical activity levels, and populations with or at increased risk of chronic diseases. In the future, delivery of both broad-based preventive messages, as well as tailored programs for particular 'at risk' groups, will help maximize population-health benefits, while minimizing the likelihood of ineffective approaches. Put simply: *how*, *why* and *where* is it important to change sitting time, and in *whom*?

Conclusion and Recommendations

In closing, further evidence is still required to inform the efficacy and specificity of sedentary behavior recommendations for clinical practice, and for public health policies aiming to reduce the burden of hypertension. Nonetheless, with the ubiquity of sedentary behaviors and the challenges for many in adhering to structured exercise guidelines, it is appropriate to advise: "*Move More, Sit Less, More Often*" to improve BP control[26, 27]. Importantly, such advice should continue to be viewed as *complementary* in the context of other health behaviors, such as the promotion of regular moderate-vigorous physical activity, improving dietary and sleep habits, and minimizing stress. In addition to improving other risk factors associated with inactivity, a "*whole-of-day*" approach to reducing sitting time and increasing daily incidental movement may prove useful in its own right for improving BP control – particularly in 'at risk' populations and for those already managing hypertension. Such a strategy may also be an acceptable "*gateway"* for those who are physically inactive and highly sedentary, overweight/obese, elderly, deconditioned, and/or unable or reluctant to add/transition directly into structured exercise.

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Figure Legends

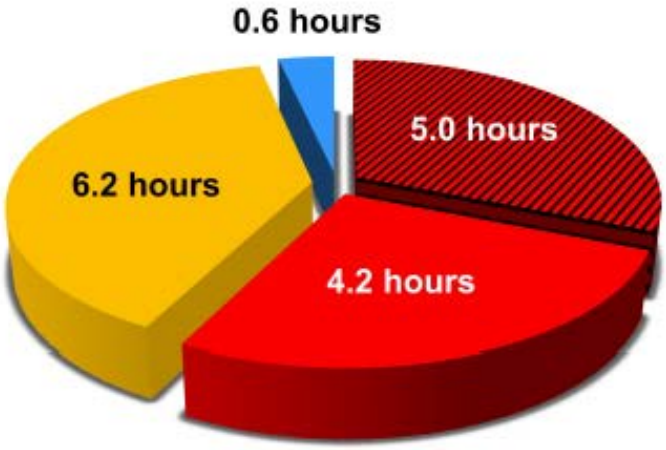
Figure 1. Unpublished data from the *AusDiab3* cohort showing how a sub-sample of Australian adults (n=717, aged 36-80 years) allocate their physically-active and sitting time during waking hours on average (derived from *both* ActiGraph™ and ActivPAL™ activity monitors and normalized to 16 hours). These data highlight the high volumes of sitting time typically observed, and the proportion of people that accumulated sitting time in "prolonged" unbroken bouts (≥30 minutes). Note that moderate-vigorous intensity activity is calculated based on every minute of activity accumulated over the day (i.e. not just in "exercise" bouts of 10 min or more).

Figure 2. Temporal changes in systolic and diastolic BP of pooled data from four separate crossover trials[39, 43, 73, 85] employing similar experimental protocols in individuals with and without hypertension. **(A)** Lines represent line of best fit (with 95% CI, dotted lines) for uninterrupted sitting (red line) and sitting interrupted with short 2-3 minute *walking breaks* (blue line) every 20-30 minutes after a 1-hour steady-state period. **(B)** Lines represent line of best fit (with 95% CI, dotted lines) for uninterrupted sitting (red line) and sitting interrupted with short 3 minute *simple resistance activities* (green line) every 30 minutes after a 1-hour steady-state period. Hypertensive individuals defined by a combination of clinical diagnosis/medication use, or BP ≥130/80 mmHg at screening visit. Solid dashed line represents new US clinical thresholds for hypertension (>130/80 mmHg)[1]. Difference in slopes according to a linear mixed effect model adjusted for age, sex, BMI, treatment order and baseline values, ****P*<0.001, ***P*=0.002 (see Supplementary Table S2 for further details on the statistical models/results).

Figure 3. Hypothesized mechanisms by which prolonged sitting may influence risk for hypertension and cardiovascular complications. Systemic reductions in metabolic demand

and blood flow, and elevated sympathetic nervous system (SNS) activity, may evoke concurrent decrements in insulin sensitivity and vascular function, promoting oxidative stress and low-grade inflammatory cascades. When prolonged sitting is habitual, these factors likely contribute to the development of hyperglycemia, dyslipidemia and hypertension, promoting vascular damage and progression towards serious cardiovascular complications. GFR, glomerular filtration rate. NOS, nitric oxide synthase.

Figure 4. Hypothesised vascular mechanisms by which prolonged sitting may impact on blood pressure in contrast to sitting interrupted by regular active breaks. During *prolonged sitting* (left side): **(a)** low metabolic/ATP demand within muscles results in low levels of vasodilator metabolites, constriction of pre-capillary arterioles, and closure of precapillary sphincters. This in turn results in blood being shunted through metarterioles. **(b)** Reduced pressure differential between capillaries and upstream muscular (distributing) arteries reduces blood flow and endothelial shear stress, promoting vasoconstriction through associated endothelial mediators (i.e., reduced nitric oxide and increased endothelin-1), and **(c)** reduced calibre of resistance arterioles, increasing peripheral resistance and BP. During *brief 2-3 minute activity bouts during prolonged sitting* (right side): **(d)** increased metabolic/ATP demand within muscles results in upregulation of vasodilator metabolites, dilation of pre-capillary arterioles and relaxation of precapillary sphincters, promoting flow through nutritive capillaries. **(e)** The greater pressure differential between capillaries and upstream muscular (distributing) arteries increases blood flow and endothelial shear stress, promoting vasodilation through associated endothelial mediators, and **(f)** increased calibre of resistance arterioles, reducing peripheral resistance and BP. Previously observed alterations in circulating noradrenaline (NA) during these two states are also depicted, along with endothelin-1 (ET-1) and nitric oxide bioavailability (NO), for which the evidence is only preliminary.

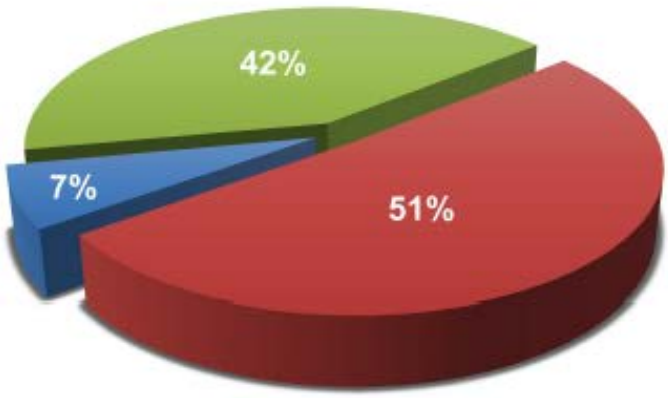


Moderate-vigorous intensity activity

Light intensity activity

Sitting in <30 min bouts

Prolonged sitting in ≥30 min bouts

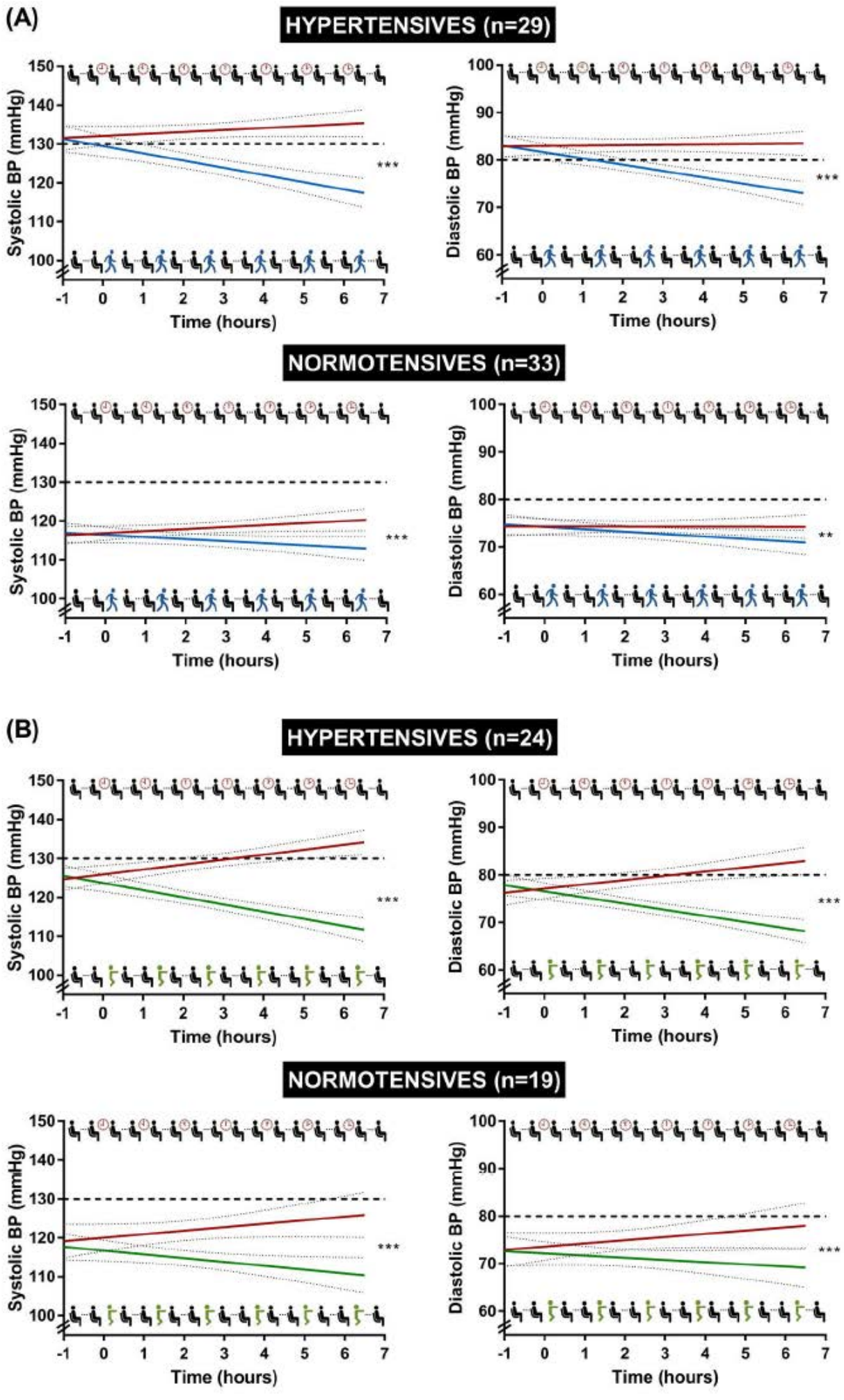


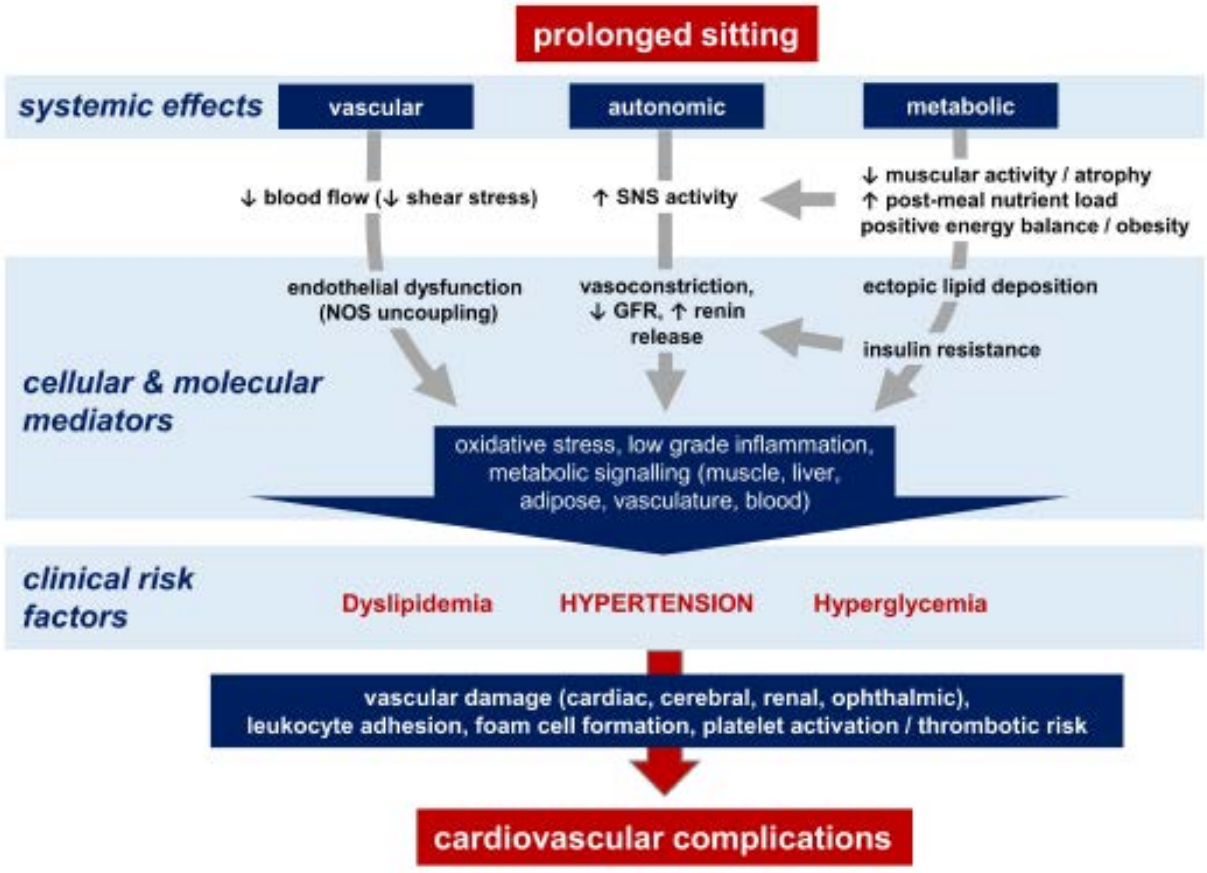
Proportion of population accumulating prolonged sitting in ≥30 min bouts totalling:

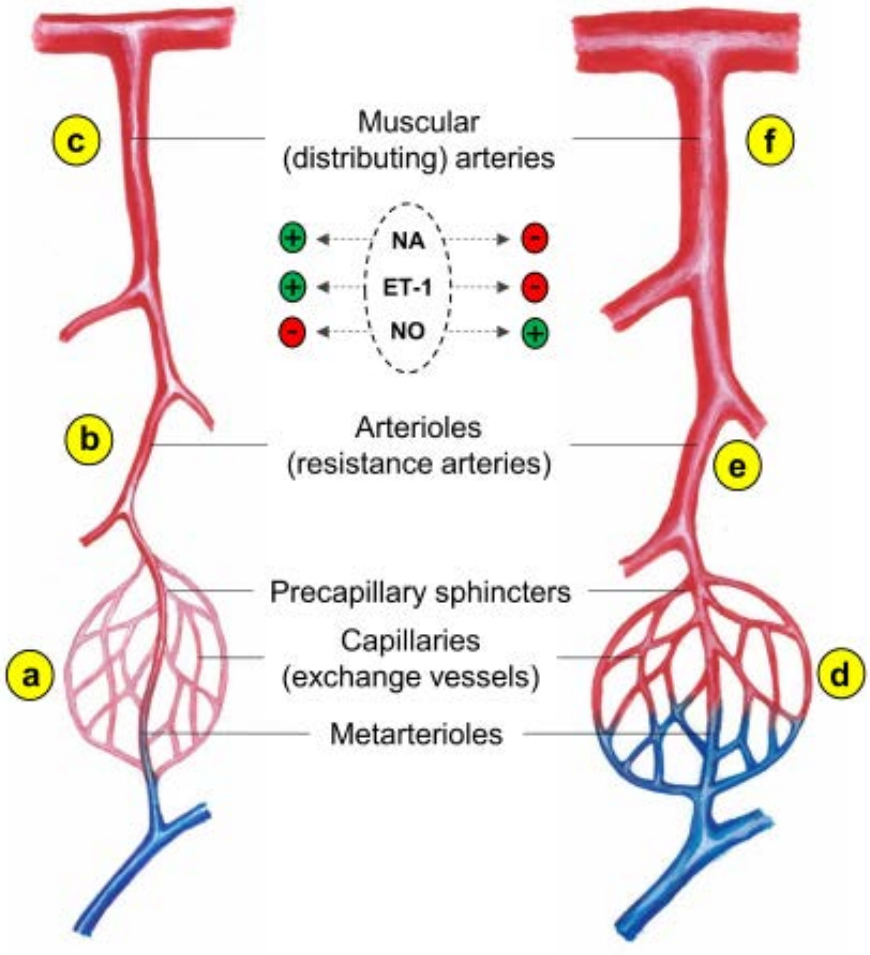
<2 h/day

2-4 h/day

>4 h/day


(A)
HYPERTENSIVES (n=29)
Systolic BP (mmHg)
Diastolic BP (mmHg)
Time (hours)
***
NORMOTENSIVES (n=33)
**
(B)
HYPERTENSIVES (n=24)
NORMOTENSIVES (n=19)


prolonged sitting
systemic effects
vascular
autonomic
metabolic
↓ blood flow (↓ shear stress)
↑ SNS activity
↓ muscular activity / atrophy
↑ post-meal nutrient load
positive energy balance / obesity
endothelial dysfunction
(NOS uncoupling)
vasoconstriction,
↓ GFR, ↑ renin
release
ectopic lipid deposition
insulin resistance
cellular & molecular
mediators
oxidative stress, low grade inflammation,
metabolic signalling (muscle, liver,
adipose, vasculature, blood)
clinical risk
factors
Dyslipidemia
HYPERTENSION
Hyperglycemia
vascular damage (cardiac, cerebral, renal, ophthalmic),
leukocyte adhesion, foam cell formation, platelet activation / thrombotic risk
cardiovascular complications


c
Muscular
(distributing) arteries
f
NA
ET-1
NO
b
Arterioles
(resistance arteries)
e
Precapillary sphincters
a
Capillaries
(exchange vessels)
d
Metarterioles