Graphical Review

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Exercise as Vascular Medicine: Can Exercise Combat Negative Health Behaviors From Causing Endothelial Dysfunction?

Austin T. Robinson,[1] Nile F. Banks,[1,2] and Nathaniel D.M. Jenkins[3,4,5]

ABSTRACT

Endothelial function is critical to cardiovascular health, regulating blood vessel function through the release of vasodilators and constrictors—namely, nitric oxide—controlling redox balance, platelet activation and aggregation, leukocyte adhesion, and proliferation of vascular smooth muscle. Vascular dysfunction, characterized by impaired endothelial function, significantly increases cardiovascular disease (CVD) risk. CVD is the leading cause of death in the United States and most of the world. Advancing age is a primary risk factor; however, several health behaviors influence vascular aging. Risk factors such as poor diet, a sedentary lifestyle, and poor sleep can reduce endothelial function, even early in life. Exercise has emerged as a protective factor that can potentially confer vascular protection in the context of negative health behaviors. In this review, we seek to address the importance of endothelial function for cardiovascular health, identify key risk factors and mechanisms that contribute to endothelial dysfunction, summarize the protective effects of exercise against endothelial dysfunction (including mechanisms), and highlight key knowledge gaps and future directions.

Keywords: cardiovascular disease, endothelial dysfunction, exercise, nitric oxide, oxidative stress

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the United States and most of the world (1). Aging is the leading risk factor for CVD, and CVD risk with aging is further amplified by the presence of modifiable comorbidities such as obesity and cardiovascular–kidney–metabolic syndrome (1,2). These comorbidities and negative health behaviors such as poor diet, sedentary lifestyle, and poor sleep also accelerate vascular aging and CVD risk (2,3). Vascular aging refers to progressive structural and functional changes in the vasculature that occur with age, including increased arterial stiffness and endothelial dysfunction. These changes are characterized by reduced nitric oxide (NO) production and bioavailability, which impairs the ability of blood vessels to dilate and effectively deliver blood to tissues (4). Together, these alterations contribute to the development and progression of CVD. Alarmingly, the declining CVD mortality rates achieved over the last few decades recently began reversing, particularly in high-income countries (5). The aging global population and rising chronic disease rates are expected to contribute to further increases in CVD prevalence over the coming decades (1,4). As we grapple with strategies to reduce the incidence of CVD, vascular endothelial function has become a critical mechanistic target.

As noted above, vascular dysfunction or vascular aging is a well-established contributor to CVD (6). Impaired vascular function includes stiffening of the large elastic arteries and endothelial dysfunction characterized by reduced NO bioavailability (4). The primary source of NO is endothelial NO synthase (eNOS). As has been discussed at length in prior reviews (6,7), there are several vasodilators beyond NO, but their contributions are often context-specific, depending on health or disease, or occur within specific vascular beds. Under healthy conditions, NO is the primary mediator of vasodilation in most vascular beds (6). Although arterial stiffening and endothelial dysfunction both contribute to impaired blood flow, increased end-organ damage, augmented cardiac afterload (leading to heart damage), and ultimately CVD risk (7,8), this review will focus specifically on endothelial dysfunction.

To develop successful interventions to prevent and reverse vascular dysfunction, we must identify contributing pathophysiological mechanisms. One such intervention is regular exercise. Regular exercise has numerous beneficial health effects across several organ systems (6,9). It is well established that regular exercise improves health span and lifespan, in part due to its beneficial effects on cardiovascular health. The benefits of exercise from a CVD-risk perspective supersede the estimated protection that would be conferred from reducing conventional risk factors alone (10).

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Emerging evidence demonstrates that exercise improves endothelial function in the context of aging and comorbidities such as obesity and hypertension (11,12), and protects against negative health behaviors such as poor diet (2,6,9). The purpose of this review is to summarize the existing data on the ability of exercise to prevent endothelial dysfunction due to negative health behaviors, including poor diet, sedentary lifestyle, and poor sleep health. We will briefly discuss methods used to assess endothelial function in humans and mechanisms contributing to endothelial dysfunction to contextualize findings and elucidate how exercise is protective. Lastly, we will highlight knowledge gaps and potential future directions.

TAKING A PULSE ON ARTERIAL HEALTH: ASSESSING ENDOTHELIAL FUNCTION

Ultrasound-based flow-mediated dilation (FMD) is the most common technique used to assess macrovascular endothelial function in humans. First described by Anderson and Mark (13), the FMD technique uses vascular ultrasonography to measure shear stress-mediated increases in conduit artery diameter induced by reactive hyperemia following an ischemic challenge, a process that is at least partially NO dependent (14). Importantly, FMD correlates strongly with coronary artery vasodilatory function and is prognostic of future CVD risk (14). Most of the data we will focus on in this paper are derived from studies using FMD.

Although a full description of microvascular function assessments is outside the scope of this review, this topic has been reviewed at length (7). Briefly, microvascular endothelial function is often assessed using non- or semi-invasive methods, such as ultrasonography or strain-gauge plethysmography, to measure forearm blood flow in response to reactive hyperemia or intra-arterial pharmacological agents. Another common technique is laser Doppler flowmetry (LDF) to assess cutaneous microvascular function. Briefly, LDF assesses variation in the frequency of Doppler shift produced by the movement of blood cells under a laser probe placed on the skin (15). LDF assessment may utilize both physiological (e.g., heating or hyperemia) and pharmacological stimuli (acetylcholine and sodium nitroprusside), typically delivered through microdialysis fibers or via iontophoresis, to evaluate blood flow dynamics and mechanisms (15). It is also pertinent to highlight that microvascular function is predictive of CVD-related events (16). For example, there are data suggesting that the reactive hyperemic response (microvascular reactivity) during

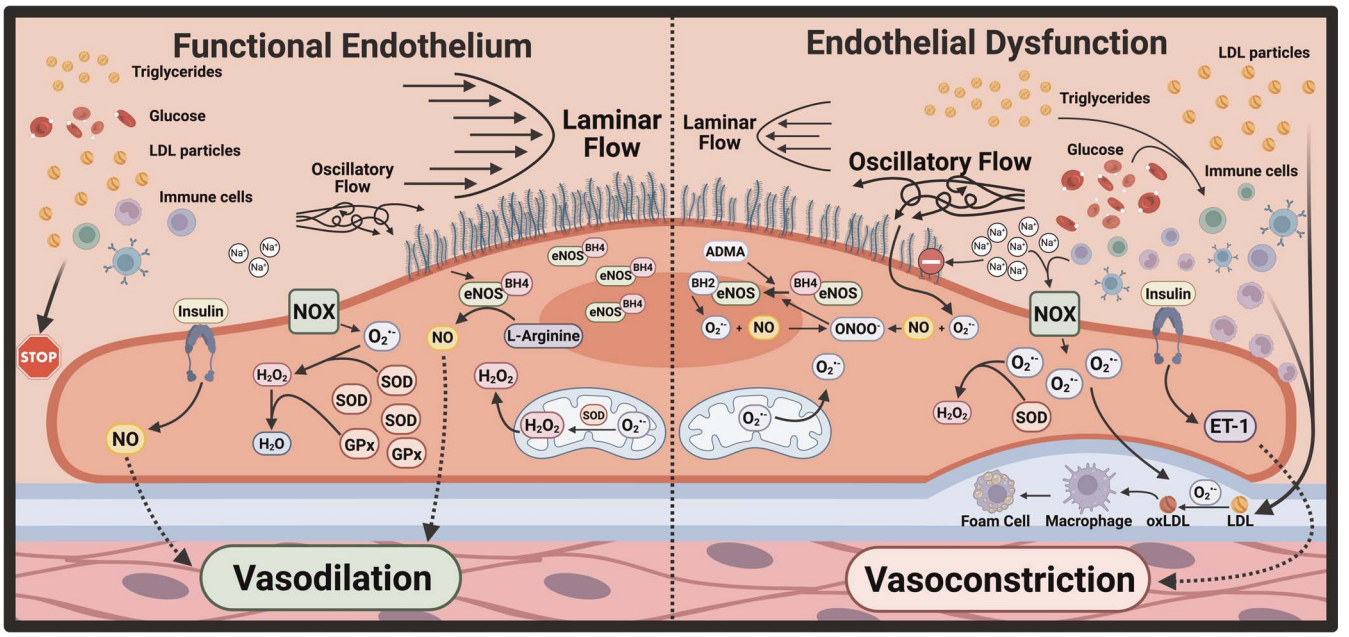

Figure 1. Comparison of functional (*left*) versus dysfunctional endothelium (*right*). Various health behaviors can promote functional endothelial health through multiple mechanisms. Exercise results in repeated increases in laminar blood flow through the arterial system and thus shear stress against the artery wall. Shear stress causes mechanotransduction at the level of the glycocalyx, a carbohydrate-rich glycoprotein sensitive to the physical displacement of hemodynamic shear stress. Stimulation of the glycocalyx results in a cell signaling cascade that upregulates nitric oxide (NO) production by endothelial NO synthase (eNOS) and L-arginine. On the other hand, oscillatory blood flow causes oxidative stress and the production of reactive oxygen species (ROS). Although ROS are vital for normal physiological function and adaptation to exercise, high levels overwhelm the endothelium's antioxidant capacity and decrease NO bioavailability. The main sources of ROS are produced by nicotinamide adenine dinucleotide phosphate oxidases (NOX) and are mitochondrial-derived ROS. Sodium (Na^+) circulating cytokines, which are elevated by high fat, sugar, and/or salt consumption, stimulate the production of ROS in the endothelium. The production of superoxide anions ($O_2^{\bullet-}$) causes direct and indirect NO bioavailability reduction. $O_2^{\bullet-}$ directly scavenges NO to produce peroxynitrite ($ONOO^-$), whereas $ONOO^-$ oxidizes tetrahydrobiopterin (BH_4) to dihydrobiopterin (BH_2). The affinity of BH_4 and BH_2 to eNOS is roughly equal, and when BH_4 is bound to eNOS, it produces NO. In contrast, when BH_2 is bound to eNOS, it produces more $O_2^{\bullet-}$, resulting in a positive feedback loop and reduction in NO levels. Asymmetric dimethylarginine (ADMA) also contributes to the reduction of eNOS. Additionally, shear stress regulates the action of insulin receptors on endothelial cells to produce either NO or endothelin-1 (ET-1). Exercise-trained individuals have higher levels of superoxide dismutase (SOD) and glutathione peroxidase (GPx), which act as antioxidants and reduce $O_2^{\bullet-}$ to hydrogen peroxide (H_2O_2) and H_2O_2 to water molecules (H_2O). High salt consumption contributes to endothelial dysfunction as well through NOX stimulation and through the reduction of SOD. The reduction of these ROS increases NO bioavailability and protects the arterial wall from foam cell production and the progression of atherosclerosis. LDL, low-density lipoprotein; oxLDL, oxidized LDL.

FMD is an even stronger predictor of CVD risk than the brachial artery dilator response (17).

BREAKING BAD: THE BIOCHEMICAL PATH TO ENDOTHELIAL DYSFUNCTION

Several mechanisms have been proposed to contribute to endothelial dysfunction, including increased production of reactive oxygen species (ROS) leading to oxidative stress (see Fig. 1). Oxidative stress characterized by greater superoxide ($O_2^{\bullet-}$) production can directly reduce NO bioavailability by scavenging free NO to form the highly reactive oxidant peroxynitrite ($ONOO^-$) (18). There are several sources of ROS production in the endothelium, including the nicotinamide adenine dinucleotide phosphate oxidase (NOX) family of enzymes, xanthine oxidase, mitochondria, lipoxygenase, and uncoupled eNOS (6,12,18,19). There is an interplay between these mechanisms and oxidative stress that plays a role in switching eNOS from a NO-producing enzyme to an $O_2^{\bullet-}$-producing enzyme via eNOS uncoupling. This process is caused in part by oxidation of the eNOS cofactor tetrahydrobiopterin to dihydrobiopterin (20). Other mechanisms of reducing NO include increased asymmetric dimethyl-L-arginine, a compound that competes with L-arginine at eNOS, resulting in reduced NO production (21). Another mechanism involves the suppression of the upstream eNOS activator phosphatidylinositol 3-kinase (22), which is particularly relevant in the context of dysregulated vascular insulin signaling caused by energy surplus from poor diet and sedentary behavior.

EXERCISE: THE HERO THE ENDOTHELIUM DID NOT KNOW IT NEEDED

Exercise reduces CVD-related and all-cause mortality in a dose-dependent manner (23). The benefits of exercise on endothelial function are imparted by habitual, transient increases in blood flow that increase laminar shear stress, eNOS activation, and NO production (6). Both resistance training (RT) and aerobic exercise training (AT) involve transient periods of ischemia during muscle contraction and sustained increases in shear stress during the bout, with the former experienced to a greater extent during RT and the latter to a greater extent during AT. Exercise counteracts many of the mechanisms discussed in the preceding section to prevent endothelial dysfunction (see Fig. 2). For example, regular exercise leads to decreased vascular NOX expression and increased expression of the endogenous antioxidant superoxide dismutase (SOD), which catalyzes the formation of $O_2^{\bullet-}$ to hydrogen peroxide (H_2O_2). Importantly, H_2O_2 is less reactive than $O_2^{\bullet-}$, can be used as an alternative vasodilator to compensate for impaired NO-mediated vasodilation in some contexts (12,24), and can be further reduced to water by the antioxidant glutathione (4). The next section will highlight several negative modifiable health behaviors that contribute to endothelial dysfunction, including poor diet, sedentary lifestyle, and poor sleep health (see Fig. 3) and will discuss evidence on the ability of exercise to counteract these factors (see Fig. 4). Apart from FMD- and LDF-based studies, several studies have used biomarkers of endothelial function (e.g.,

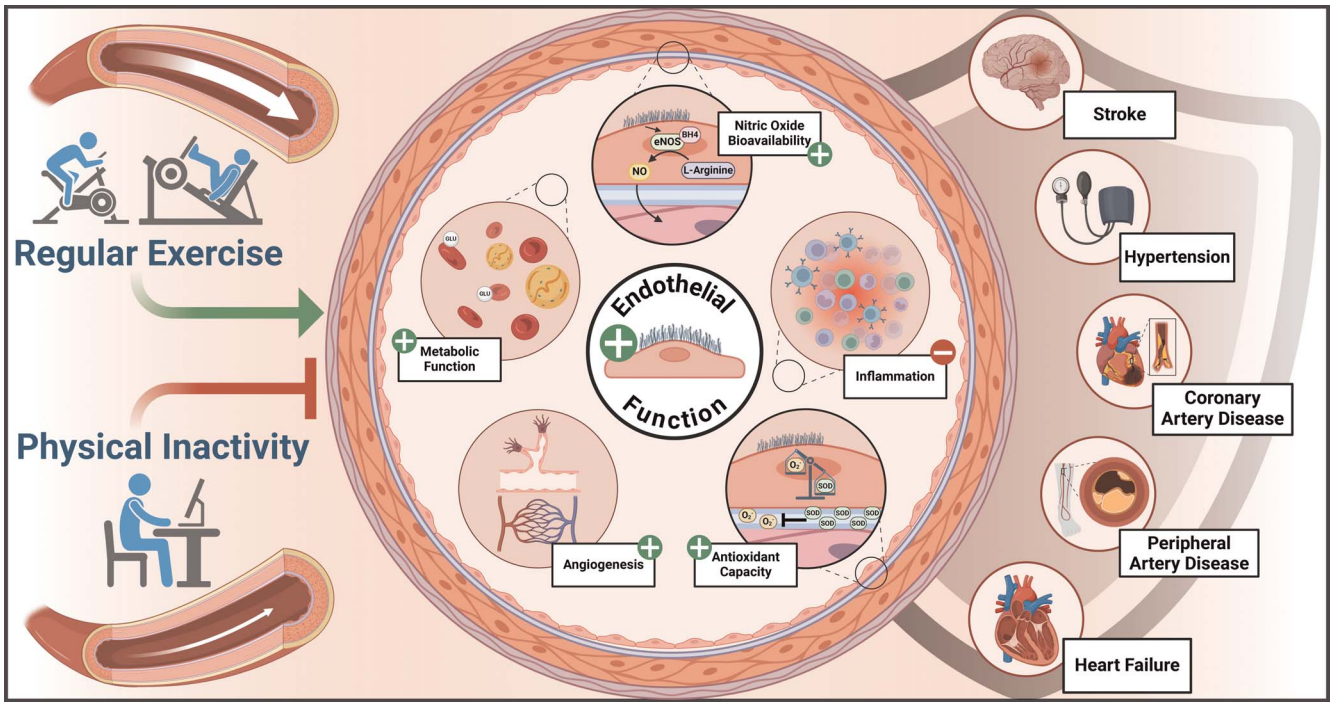

Figure 2. Regular exercise and physical activity increase blood flow within the arteries. This increase in blood flow subjects the endothelial cells, which line the inner wall of the artery, to a frictional force called shear stress. Shear stress triggers a cascade of downstream cellular mechanisms that result in improved nitric oxide (NO) bioavailability, reduced inflammation, increased antioxidant capacity, angiogenesis, and improved metabolic function. The sum of these effects reduces an individual's risk for multiple cardiovascular diseases. On the other hand, physical inactivity results in drastically lower levels of shear stress and thus the opposite effect. BH4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; GLU, glucose; O_2^-, superoxide; SOD, superoxide dismutase.

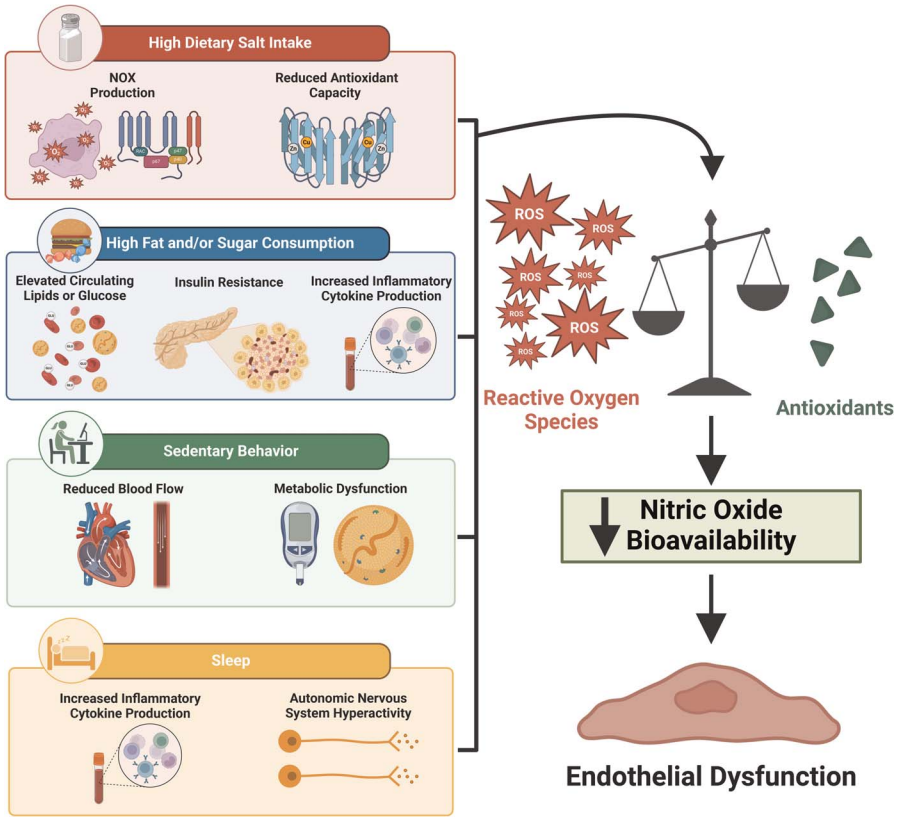

Figure 3. Negative health behaviors that contribute to vascular endothelial dysfunction. There are several negative physiological processes that result from these lifestyle factors, and they all result in the overproduction of reactive oxygen species (ROS) and decreased antioxidant capacity. The imbalance between ROS and antioxidants results in oxidative stress, which reduces nitric oxide bioavailability and results in endothelial dysfunction. Cu, copper; GLU, glucose; NOX, nicotinamide adenine dinucleotide phosphate oxidase; O_2^-, superoxide; RAC, Ras-related C3 botulinum toxin substrate; Zn, zinc.

endothelial progenitor cells) in multiple clinical populations suffering from cardiometabolic diseases to demonstrate the efficacy of exercise for improving vascular health (25).

ENDOTHELIAL SABOTAGE: HOW PROCESSED FOODS UNDERMINE VASCULAR HEALTH

Processed foods account for nearly 60% of energy intake in the American diet and are linked to increased CVD risk factors, such as obesity and hypertension (2). There are many facets of processed foods that make them unhealthful, but in the context of this review, we will specifically focus on their high salt, added sugar, and fat contents. High salt, sugar, and added fat, common components of processed foods, negatively impact endothelial function (2). These dietary factors contribute to vascular dysfunction by increasing oxidative stress and reducing NO bioavailability (see Fig. 3) (3).

High dietary salt reduces vascular function in rodents and humans, including large and small artery function (reviewed in depth previously (2,19)). High dietary salt impairs vascular function through several mechanisms, but notable pathways include increasing oxidative stress and reducing NO bioavailability. Briefly, high salt intake increases vascular oxidative stress, which results in NO being scavenged to form $ONOO^-$ (see Fig. 1), and can disrupt the glycocalyx which results in less shear stress-induced NO production. Specifically, rodent data indicate that high dietary salt increases NOX expression (26). Additionally, high dietary salt suppresses angiotensin II, a transcription factor for SOD (19). Evidence linking high dietary salt to oxidative stress and reduced NO bioavailability, both of which cause endothelial dysfunction, is consistently demonstrated in human studies. For example, apocynin (antioxidant) and tempol (SOD mimetic) prevent high-dietary-salt-induced reductions in cutaneous vasodilator function assessed via LDF (2). Also, high dietary salt blunts microcirculatory responses to eNOS inhibition, suggesting reduced NO bioavailability (2).

Cross-sectional data suggest that habitual physical activity (self-reported) is inversely related to salt-sensitive blood pressure and several months of AT reduces the incidence of salt-sensitive blood pressure in older adults with hypertension (27,28). To our knowledge, there are no human data on the protective effects of exercise against high salt on the endothelium. However, voluntary wheel running in rodents prevents high-dietary-sodium-induced endothelial dysfunction and arterial stiffening (26). The mechanisms included AT preventing increases in NOX and decreases in SOD expression within the vasculature (26). Additional studies are needed to determine whether these findings translate to human participants and whether RT protects against high-salt-induced endothelial dysfunction.

The effect of acute meal consumption on brachial artery FMD has been well summarized (29). Acute consumption of complex carbohydrate- and fat-rich foods generally regarded as healthful, such as whole grains and nuts, does not appear to reduce FMD

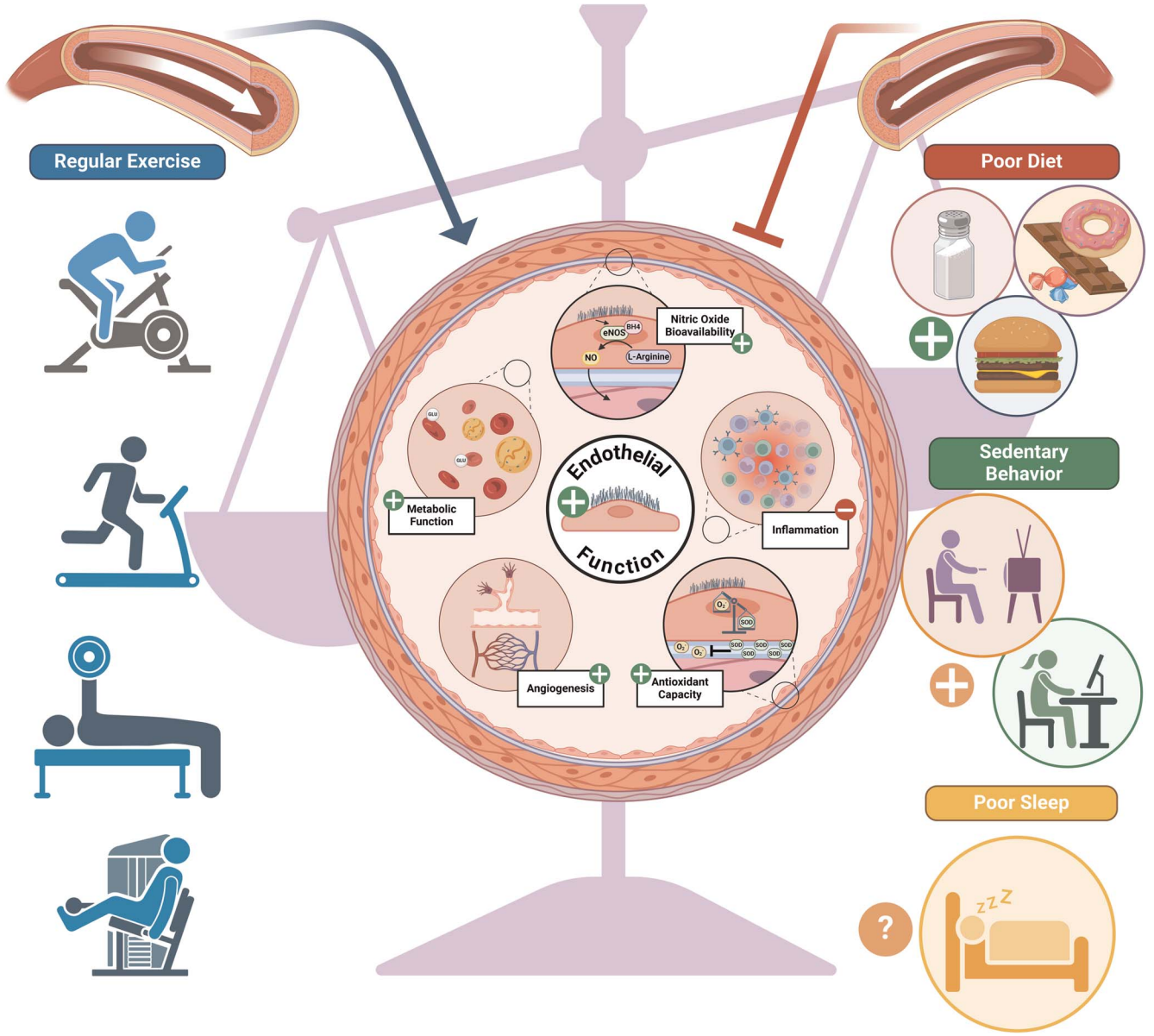

Figure 4. The role of exercise in counteracting the effects of negative health behaviors on endothelial function. Although strong evidence supports the ability of exercise to counteract the vascular impairments induced by high-fat and high-sugar diets, there is limited to moderate evidence suggesting that exercise can offset the effects of high dietary salt intake and a sedentary lifestyle. There is scant evidence that exercise can counteract the adverse vascular effects of poor sleep quality or duration. These findings highlight the need for further research on the role of exercise as a protective intervention against lifestyle-driven endothelial dysfunction. BH4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; GLU, glucose; NO, nitric oxide; O_2^-, superoxide; SOD, superoxide dismutase.

(3,30). However, acute consumption of meals high in simple sugars and added dietary fat (e.g., processed food with added oils) reduce FMD via a combination of hyperglycemia and hyperlipidemia, vascular oxidative stress and inflammation, and reduced NO bioavailability (see (3)). Regarding the ability of exercise to counteract high-sugar and high-fat consumption, acute AT several hours prior to consuming a high-sugar meal prevents reduced endothelial function (3). Both acute moderate- and high-intensity aerobic interval exercises prevent postprandial FMD impairment following a high-fat mixed meal (3). Although not specific to endothelial function, acute RT prevents increased arterial stiffness following a high-fat mixed meal, an effect likely mediated by blunting transient functional changes, such as heightened sympathetic outflow influencing vascular tone, rather than by immediate structural alterations in the arterial wall. Our group was among the first to demonstrate that regular exercisers, whether primarily engaged in AT, RT, or cross-training, appeared to be protected against postprandial reduction in FMD following an ultra-processed, high-sugar, high-fat mixed meal (3).

SITTING DUCKS: SEDENTARY BEHAVIOR WREAKS HAVOC ON ENDOTHELIAL CELL HEALTH

Sedentary behavior is defined as any waking activity in a sitting or reclined position with an energy expenditure ≤1.5 metabolic equivalents, and its cardiovascular consequences have been known since

the 1950s when seminal work reported bus drivers exhibited twice the CVD incidence of bus conductors (31). In the past several decades, sedentary time has increased and physical activity rates have decreased due to the modern nature of transportation, work, and social settings. Importantly, one can exercise daily and still lead an overall sedentary lifestyle (32). For example, someone who goes to the gym for an hour each morning but then spends the rest of the day sitting in their car, at a desk, and on a couch/recliner would be classified as a sedentary habitual exerciser. The high amount of sedentary behavior in this scenario still poses a risk compared to leading a more active life outside of the gym (32), likely due to excess sitting, as noted in a previous review (33). Indeed, evidence from more than one million adults indicates that physical activity eliminates the increased mortality risk associated with sedentary behavior only if at least 60–75 $min \cdot d^{-1}$ of moderate-intensity activity is performed, which is three times greater than current physical activity recommendations (34).

As little as 1 h of sedentary behavior results in a reduction in laminar shear stress (33), leading to a physiological cascade resulting in transiently impaired endothelial function. However, there are findings that apparently young and healthy female participants may be protected from endothelial dysfunction after prolonged sitting compared with age-matched male participants (35). Similar studies are needed in older adults because the protection may not exist in postmenopausal females. Nonetheless, sedentary behavior results in additional metabolic disturbances, including vascular insulin resistance, hyperglycemia, and dyslipidemia, all of which exacerbate endothelial dysfunction (33). Because reductions in endothelial shear stress due to sedentary behavior are thought to cause impairments in endothelial function, augmenting endothelial shear stress patterns holds promise as an effective strategy to improve endothelial function and augment nutrient-stimulated skeletal muscle blood flow (36). Interestingly, the interruption of sedentary behavior by periodic movements, such as just a few minutes of body-weight RT, walking, or fidgeting, can effectively combat the detrimental effects of sedentary behavior on vascular endothelial function (33,37). Generally speaking, shear stress is the most important factor when combating the effects of sedentary behavior on endothelial function (38), so any activity that disrupts long periods of low shear stress (e.g., leg heating) likely will improve endothelial function and long-term cardiovascular health (see Fig. 4). Nonetheless, due to the pluripotent benefits of physical activity, we would recommend strategies that periodically result in physical activity, if possible.

RESTLESS NIGHTS, TROUBLED VESSELS: IMPACT OF POOR SLEEP ON ENDOTHELIAL HEALTH

Sleep is essential for health, yet nearly one-third of US adults sleep less than the recommended 7–9 h per night and 30% experience insomnia, characterized by difficulty falling asleep, nighttime awakenings, and early waking (39,40). There are multiple dimensions of sleep, such as sleep duration (time spent asleep), efficiency (percentage of time spent asleep relative to the total time spent in bed), and variability (fluctuations in sleep patterns over time, including changes in sleep duration, bedtime, wake time, and sleep efficiency from night to night). Short sleep duration, poor sleep efficiency, and high sleep variability have collectively been linked to increased cardiometabolic disease risk (e.g., CVD, cardiovascular–kidney–metabolic syndrome, type 2 diabetes), whether it be premature endothelial dysfunction in younger to middle-aged adults or increased risk of disease outcomes (39–41). Thus, a growing body of evidence has sought to examine the mechanisms by which these sleep behaviors may promote increased CVD risk, with a focus on the vascular endothelium as a potential pathophysiological nexus.

Interestingly, both micro- and macrovascular endothelial functions are reduced by total sleep deprivation, such as 24 h without sleep, but appear to be relatively resistant to acute experimental manipulation of sleep duration using partial sleep restriction over short durations (e.g., 1–2 nights) (42). Evidence from well-controlled experimental studies using short-term to chronic partial sleep restriction (i.e., 8 d–6 wk) has mostly demonstrated that short sleep leads to impaired FMD (see Shah et al. (41)). These functional impairments are accompanied by increased endothelial inflammation (nuclear factor-kappa B nuclear fluorescence) in isolated, venous endothelial cells (41). Exercise may protect against poor sleep in the first place, or exercise may protect endothelial function in the context of poor sleep, but there are very limited data regarding the latter.

There is strong evidence to suggest that exercise decreases sleep onset time and increases sleep health (43). Exercise represents a powerful stimulus that regulates circadian rhythms or zeitgeber (reviewed briefly in Rogers et al. (39)), and because variability in sleep timing may increase CVD risk by disruption to circadian entrainment, it stands to reason that exercise could help with sleep variability. However, it is unclear whether exercise-related effects on poor sleep health (i.e., duration, efficiency, variability) extend to protecting endothelial function (see Fig. 4). Some preliminary evidence exists to suggest that exercise may decrease markers of endothelial activation and adhesion proteins in night shift workers (44). Additionally, epidemiologic data from the United Kingdom Biobank cohort suggest that middle-aged and older adults with short sleep (defined as <6 h per night) are at increased risk for all-cause and CVD-related death (45). However, this risk is attenuated among individuals who achieve objectively measured physical activity in accordance with World Health Organization guidelines (45). Given the scant data on exercise and endothelial function specifically, future experimental studies are needed to examine the ability of exercise to prevent or restore vascular function in the face of poor sleep, with careful consideration of the different dimensions of sleep, such as duration and variability. For example, studies examining whether habitual exercise can improve endothelial function in individuals with substantial variability in sleep timing, such as shift workers, will be an important avenue for future research.

CONCLUSION

Endothelial dysfunction is a key antecedent of CVD. As the leading cause of death worldwide, CVD prevention requires targeted strategies to maintain vascular health across the lifespan and in varied life circumstances. Regular exercise is a powerful intervention, improving endothelial function through mechanisms that enhance NO bioavailability and reduce inflammation and oxidative stress. By addressing endothelial dysfunction directly, exercise helps mitigate both the onset and progression of CVD, supporting its role as a cornerstone of cardiovascular health. Despite the robust evidence supporting exercise as a protective strategy against endothelial dysfunction, several important questions remain. Future work should examine the optimal types, intensities, and volumes of exercise needed to mitigate endothelial dysfunction in populations with distinct risk profiles, such as older adults, individuals with obesity, and those with less modifiable yet poor sleep (e.g., shift workers). Additionally, more research is needed to clarify how sex and gender differences influence the vascular benefits of exercise in the context of other negative health behaviors. For instance, future work

prioritizing understanding how the menopause transition influences sleep-related endothelial dysfunction is needed because this period represents a particularly vulnerable time for female cardiovascular health. Investigating whether exercise can mitigate vascular impairments during this transitional stage may be especially valuable. Finally, mechanistic studies linking molecular changes within the endothelium to clinically meaningful improvements in vascular function will help refine exercise prescriptions and identify complementary therapies to further enhance cardiovascular health.

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