REVIEW ARTICLE

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The Physiological Aspects of Exercise-induced Adaptation in the Cardiovascular System

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ABSTRACT

Low exercise and a sedentary lifestyle are independently attributed to a rise in the level of morbidity and mortality. In the past four decades, explosive progress in knowledge and application has been made in the field of exercise physiology. Exercise can be regarded as an evolutionary stimulus for ameliorating human cardiovascular health. Several studies showed that heart attack patients who implement a formal exercise program can have a reduced death rate of 20–25%. The cardiovascular beneficial effects of regular physical activity are suggested mainly due to the exercise-induced changes in different cardiovascular risk factors such as obesity, dyslipidemia, and high blood pressure. We conducted an extensive literature search on various electronic databases such as PubMed, Science Direct, Scopus, and Web of Science. This review aimed at providing further advancement of our understanding of how different cardiovascular aspects can be modulated by exercise which could be considered as novel therapeutic strategies to prevent or treat different cardiovascular disorders. The present knowledge regarding exercise-induced cardiovascular adaptation, including processes and bioactive substances, has been improved, but many molecular/cellular aspects remain to be elucidated.

Keywords: Adaptation; Atherosclerosis; Cardiovascular physiology; Cardiovascular risk factors; Exercise.

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INTRODUCTION

The modern lifestyle has led to decreased physical activity as well as dependency on machines instead of performing some day-to-day activities such as walking. Although many comforts have been acquired from this lifestyle, a disadvantageous impact has been reported on the health of humans, which has raised big concerns about public health [1]. Unfortunately, the impact of this sedentary lifestyle is aggravated by non-healthy diet regimens containing, for instance, fast food and high-fat diet. This led to a rise in obesity rates in many countries of the world which consequently, resulted in alarming increased morbidity and mortality due to the high incidence of several critical diseases such as cardiovascular problems, diabetes, inflammatory diseases and cancer [2].

World Health Organization (WHO) announced that lack of physical activity is the fourth leading cause of mortality in the world [3]. In addition to this deterioration in health and wellbeing, this situation puts a big economic burden on the governments to deal with those people with sedentary lifestyles and in exercise promotion programs. It has been confirmed that physical activity/exercise can enhance quality of life and reduce the risk of incidence and progression of different pathological conditions.

This review aimed to provide a comprehensive view of the impact of exercise on the cardiovascular system physiology and show whether this physical activity could be a substantial therapeutic strategy to prevent or treat different cardiovascular disorders.

IMPACT OF EXERCISE ON GENERAL HEALTH

Physical activity has numerous physiological benefits for overall health status. The effects of proper and regular exercise on muscle, bone, and mood are chosen as examples.

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Muscular function, maximal oxygen consumption, and aerobic capacity are improved by exercise, which enhances performing regular daily activities with less fatigue, and more endurance performance [4]. In older patients with sarcopenia, although exercise could not increase the muscle mass of the upper extremities, regular physical activity could enhance muscular function and physical performance [5]. Furthermore, proper physical activity can attenuate age-related deterioration in muscle strength and mass, as well as improve muscle metabolism [6].

Physical exercise could be an efficient way to stimulate osteogenesis and decrease the risk of osteoporosis [7]. Howe and coworkers found that there is a small, statistically significant, but potentially important, advantageous effect of physical activity on bone density in postmenopausal women in comparison with the control group [8]. The authors suggested that exercise aids in avoiding bone loss in postmenopausal women. However, not all types of exercise can have the same beneficial effect on bone mass density (BMD). Weight-bearing aerobic exercises (e.g., walking) alone could not improve BMD unless they reached a considerable level of mechanical stress. Additionally, strength and resistance exercises (e.g., weight lifting and cycling) should have sufficient joint reaction force and muscle strengthening to confer a positive effect on BMD [9].

Physical activity is also known to play a crucial role in enhancing mental health and mood status. A study performed on physical education students showed that leisure, Vigor, and mood status are positively correlated with physical activity levels [10]. The authors proposed that individuals can improve their mood status and health-related quality of life by increasing their leisure time's physical activity. A recent study by Pham et al. concluded that a better mood can result from engaging in leisure time physical activities because this type of exercise could increase emotional well-being-positive effect in diabetic patients [11]. In addition, another study found that being physically active, even at a low level, can lead to major health benefits and substantially reduce the risks of depression [12].

IMPACT OF EXERCISE ON CARDIOVASCULAR RISK FACTORS

There are five major risk factors for cardiovascular disorders, including a sedentary lifestyle, hypertension, dyslipidemia, smoking, and obesity. Treating or preventing these risk factors is fundamental to reducing the potential incidence of heart attacks, strokes, and their associated death rates. Several studies have found that a regular exercise program can decrease the mortality rate by 20–25% in cardiovascular patients, as physical exercise has a beneficial effect in mitigating all risk factors [13].

A meta-analytic investigation found that exercise can reduce blood pressure (BP) in the hours after an exercise session, regardless of the individual and exercise features. However, the exercise-induced hypotensive effect was superior when the already physically active participants performed the exercise as a preventive strategy [14]. A recent meta-analysis study found that each 30 min/week of aerobic physical activity could decrease both systolic and diastolic BP by 1.78 mmHg and 1.23 mmHg, respectively. In addition, the authors realized that a reduction in BP was dose-dependent, with the greatest reduction obtained at 150 min/week [15]. However, the underlying mechanism of exercise-induced hypotension is still unclear. It has been found that baseline cardiovascular variables and endothelium-derived vasoconstrictors are involved in this hypotensive effect, while nitric oxide (NO) / endothelin-1 (ET-1) specifically may not have a role [16].

Prospective intervention studies and epidemiological studies indicated that exercise training can improve lipid profiles and eventually, reduce cardiovascular morbidity and mortality [17]. There is a clear relationship recognized between physical activity and elevation of high-density lipoprotein (HDL) as well as the reduction of both triglyceride and LDL (low-density lipoprotein)-cholesterol [18]. Small atherogenic LDL particles are also diminished by exercise [19]. Research showed that bidirectional interactions have been established between dyslipidemia and inflammatory processes. Interestingly, exercise also has been recognized to improve lipid profile by inducing anti-inflammatory effects such as altered leukocyte subtypes and cytokine patterns [20].

Furthermore, even though exercise may have a minor role in improving some cardiovascular risk factors, adding some other lifestyle modifications (such as healthy nutrition and quitting smoking) can result in a dramatic enhancement of cardiovascular health.

EXERCISE AND CARDIOVASCULAR HEALTH

Effect of Exercise on Angiogenesis

Myocardial ischemic injury and pathological cardiac hypertrophy have been well-established to be associated with inadequate angiogenesis. On the other hand, exercise-induced skeletal muscle angiogenesis is one of the important physiological adaptations that happen as a result of physical training. The latter can enhance endurance performance, in addition to amelioration in cardiovascular and skeletal muscle health. The increase in capillary density enhances waste extraction and diffusive oxygen exchange, leading to higher fatigue resistance. In addition, this angiogenesis augments muscular glucose uptake and improves metabolic and cardiovascular health [21].

A recent study found that both high-intensity interval training (HIIT) and combined HIIT with strength training could increase the expression of angiogenesis-related factors such as vascular endothelial growth factor (VEGF) and its receptor in the skeletal muscles of patients with heart failure [22]. Furthermore, a recent meta-analysis examined the impact of exercise on various peripheral angiogenesis markers, revealing a change only in VEGF and e-selectin (CD62E), with an increase in VEGF and a decrease in e-selectin following exercise. In contrast, no change has been reported in other angiogenesis markers after exercise, such as endostatin, fibroblast growth factor 2, and matrix metallopeptidase-9 [23].

Another study showed that although different types of regular exercise training, including aerobic, resistance, and combined exercises, could enhance cardiovascular health, aerobic exercise was the most effective in stimulating angiogenic responses in the myocardium of aged rats [24]. It has been suggested that cardiac endothelium-derived NO has a crucial role in exercise-induced cardiac angiogenesis. Upon exercise, the delivery of required oxygen and nutrients and physiological cardiac hypertrophy are facilitated by exercise training due to the relaxation of the coronary vasculature and the induction of proportional angiogenesis [25]. Also, HIF-1α, PGC-1α, and CD34+ are other angiogenesis proteins that have been shown to play a big part in stimulating angiogenesis in the myocardium of Wistar rats after different levels of exercise. [26]. Moreover, lymphangiogenesis, which can also

be induced by exercise [27], has an important effect on preventing different cardiovascular diseases such as myocardial injury, myocardial infarction, and heart failure [28].

Effect of Exercise on Oxidative Stress in Cardiovascular System

Oxidative damage can happen at both the molecular and cellular levels when there is an imbalance and excess of oxidants over antioxidant processes. Reactive oxygen species (ROS) are considered the significant deteriorating players that cause oxidative stress. Although low levels of ROS are fundamental for the organism acting, as signalling molecules to ensure normal cell and cardiovascular function, high levels of ROS provoke oxidative damage, and play a crucial role in the onset and progression of cardiovascular diseases [29].

On one hand, studies showed that physical activity interventions could mitigate inflammation and oxidative stress at both the cellular and tissue levels, which limits cardiovascular pathological alterations and decreases the risk of dysfunctional outcomes [30]. Additionally, endurance training has been proven to increase cardiorespiratory fitness (CRF) by enhancing antioxidant status [31]. Greater synthesis and release of antioxidants (nitric oxide and glutathiones) were noticed after some sessions of physical activity in comparison with the baseline [32].

On the other hand, exercise can increase oxidative damage in older people, making antioxidant supplementation highly recommended for those who exercise [33]. The same authors found that regular and moderate exercise is still a beneficial strategy for reducing some cardiovascular risk factors (e.g., arterial pressure and lipid profile) and preventing cardiovascular diseases. They declared that concurrent antioxidant supplementation can modulate oxidative damage and increase the beneficial effects exercise in older people. Exercise intensity generally contributes more significantly to physiological adjustments than exercise duration. It was found that biomarkers for both pro-oxidation (malondialdehyde) and pro-inflammation (tumour necrosis factor receptor) were higher after 30 minutes of moderate exercise compared to 30 minutes and 45 minutes of low-intensity exercise [34]. Furthermore, another study found that an acute cardiopulmonary exercise test can lead to an increase in oxidative stress markers and a poor prognosis for patients with heart failure. The authors recommended evaluating changes in markers of oxidative stress to determine the optimum exercise intensity for those patient [35].

However, to explain this variance in results, it has been found that an acute bout of physical activity training could temporarily increase ROS and stimulate oxidative damage and an inflammatory response. This effect is proportional to the intensity of physical activity and inversely proportional to an individual's physical conditioning status. In contrast, regular, chronic exercise can improve the antioxidant defence mechanism and lower oxidative damage [36]. Collectively, these evidences suggest that regular physical activity training is a promising and pivotal step in the treatment and prevention of cardiovascular diseases.

Effect of Exercise on Vascular Tone

While acute exercise results in alterations in vascular function instantly, regular, repeated bouts of exercise can lead to persistent physiological adaptation and structural changes in blood vessels. These functional and structural alterations depend on the features of the training load and could be influenced by exercise-derived oxidative stress and inflammation. There are primary and secondary mechanisms for the impact of exercise on the vascular system, in that repeated hemodynamic stimulation that happens during each bout of physical activity has a direct effect on the arterial blood flow, shear stress, and mechanotransduction [37].

Green et al. (1994), were the first to suggest the potential modification of endothelial function after exercise training in humans [38]. After exercise training, NO-mediated function is improved especially in the endothelial cells in both conduit and resistance arteries. This improvement is higher when there is pre-impaired endothelial function and is accompanied by structural vascular enlargement [39]. Exercise can increase blood flow through different mechanisms including the direct effect on vascular function and structure. Shear stress stimulates the maintenance of endothelial barrier function by increasing the vascular expression of NO synthase and release of NO which leads to an increase in endothelium-dependant vasorelaxation and reduces several processes in atherogenesis and restenosis [40]. In addition, physical activity can reduce the endothelial angiotensin II type 1 receptor expression which in turn causes a reduction in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and ROS production and preserves NO bioavailability [41]. These beneficial adaptations could reduce the pathological process of vascular remodelling in hypertensive patients [37].

Moreover, the exercise has other advantageous mechanisms, which include a decrease in circulating levels of endothelin-1 [42] as well as improved balance between prostacyclin and thromboxane levels in skeletal muscle [43]. However, a study by Goto et al., revealed that only aerobic exercise of moderate intensity could improve endothelium-derived vasorelaxation in humans through induced NO bioavailability, while physical activity of high intensity can paradoxically increase oxidative stress [44]. Peak reactive hyperemic blood flow has been increased by exercise in many case-control and follow-up studies [45]. Other studies used an imaging approach to show that exercise can induce arterial enlargement [46], while additional studies linked the prolonged sedentary lifestyle with the correlated inward remodelling [47]. Vascular wall thickness is increased, and the wall: lumen ratio [46] and smooth muscle contractile state [48] are changed as a result of exercise training.

Effect of Exercise on Resting Heart Rate and Blood Pressure

Exercise increases the heart rate due to parasympathetic withdrawal and augmented sympathetic activity, which is a normal response to the increased demand of tissues for oxygen and energy during physical activity. In comparison to non-athletes, athletes can easily reach their maximum heart rates during heavy exercise.

Regular exercise leads to physiological adaptations in the cardiovascular system, including strengthening of the myocardium, increasing stroke volume (ejecting more blood with each beat), and increasing delivery of oxygen to the tissues. This leads to a decrease in the resting heart rate (RHR), required to maintain adequate blood flow throughout the body. Although different mechanisms are suggested to be involved in maintaining lower RHR such as elevated parasympathetic tone and reduced responsiveness to β-adrenergic stimulation, reduced intrinsic heart rate is reported as the most likely

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mechanism responsible for the decline in RHR in those performing long-term exercise training [49]. RHR is positively correlated with mortality. A meta-analysis declared that RHR can be decreased by all types of sports, especially endurance training and yoga, in both sexes. This has a potentially advantageous effect in reducing all-cause mortality [50]. However, a cohort study examined the link between physical activity, RHR, and atrial fibrillation (AF) and found that only moderate physical activity had a beneficial effect in reducing RHR and AF, whereas vigorous physical activity may raise AF risk by different contradictory pathophysiological mechanism [51].

Long-term aerobic exercise could evoke expression of eNOS and decrease BP in 29-week-old rats. It is declared that this antihypertensive effect was via inhibition of insulin-like growth factor-1 (IGF-1), phosphorylated protein kinase B (p-Akt), and PI3K [52]. Additionally, exercise has another beneficial modulating effect on hypertension by ameliorating tunica intima, media, and adventitia thickening and fibrosis [37]. Higashi and coworkers found that regular aerobic physical activity can enhance endothelium-dependent vascular dilation in patients with mild primary hypertension compared to untrained individuals [53]. In addition, the results of the rheovasography of a study on the thigh region of subjects regularly playing sports and nonathletes with initial stages of hypertension showed that an augmented vascular wall rigidity was recorded in subjects with hypertension. Furthermore, regular physical activity could improve endothelium-dependent vascular dilation, and eventually, hypertension [54]. Moreover, in young patients with prehypertension, 8-week resistance or endurance exercise enhanced endothelial function of calf and forearm resistance arteries and improved oxidant/antioxidant balance [55]. The latter effect could be due to inhibition of vascular NADPH oxidases or stimulation of superoxide dismutase expression [56].

EXERCISE AND CORONARY ATHEROSCLEROSIS

Physical activity could reduce the risk of coronary artery disease (CAD) because it has been proven that raised levels of circulating HDL and reduced levels of triglyceride is attributed to endurance training [57]. However, the type, intensity, and duration of physical activity are important in determining the beneficial effect on the lipid profile [58]. In a dose-dependent manner, exercise can lead to a decline in plasma levels of LDL, very low-density lipoprotein (VLDL), and triglycerides and an increase in HDL levels [59]. This dose-dependent effect of exercise has been confirmed by another study in which a significant elevation in HDL and efflux capacity is reported only in the high-amount/high-intensity exercise groups [60].

In addition, the homeostasis of the arterial wall could be affected by physical activity, as people with active lifestyles showed antagonism in the development of atherosclerotic disease and reduction of CAD in comparison with sedentary subjects [61]. A prospective study showed a beneficial impact of lifetime physical activity on atherosclerosis by enhancement of coronary artery calcification, the carotid intima-media thickness, and the reactive hyperemia index [62].

eNOS expression was elevated, and neointimal formation was inhibited after injury to carotid arteries in exercised ApoE-/- mice compared with sedentary control mice [63]. In addition, exercised mice showed improved endothelial function and less lesion formation, which may be attributed to decreased vascular lipid peroxidation and superoxide levels in comparison with sedentary mice [64]. In a cross-sectional study, authors suggested that physical activity is crucial for carotid vascular health because carotid intima-media thickness, carotid plaque, and abnormal carotid artery were inversely linked to physical activity, especially in elderly people (age $\geq$ 60 years) [65]. A cohort study of 8986 male adolescents showed that a combination of high muscular strength and high cardiorespiratory fitness contributed to diminished coronary atherosclerosis, especially severe coronary stenosis [66].

However, a study showed that there is no more favourable composition of coronary plaque in lifelong endurance athletes compared to healthy lifestyle individuals as the lifelong endurance sport participants had more coronary plaques, including more non-calcified plaques [67]. Another evidence has suggested that a higher prevalence of coronary artery calcification and atherosclerotic plaques was noticed in athletes compared with controls, and atherosclerotic plaque development was higher in the most active athletes compared with less active athletes. However, athletes have a more benign composition of atherosclerotic plaques, as their plaque morphology often displays calcified plaques and fewer mixed plaques [68].

In summary, it seems that physical activity can prevent atherosclerotic diseases due to the accumulating recent studies and, perhaps at least due to inhibiting cardiovascular risk factors such as high triglyceride levels, low HDL-C, high BP, hyperglycemia, and central obesity [69]. It is important to encourage people to exercise as a therapeutic modality against atherosclerosis but in selected patients with CVD, exercise testing is critical before performing vigorous exercise.

Effect of Exercise on Electrical Adaptation in the Heart

The movement of ions in and out of the cell membrane occurs through specific pore-forming proteins called ion channels. There are many ion channels expressed in both vascular smooth muscle cells and endothelial cells. These ion channels open and close in response to activation by shear stress and cycle stretching [70].

Chen and co-workers have studied the effect of exercise training on the mesenteric arteries of spontaneously hypertensive rats, and they found that $Ca_v1.2$ current density and the expression of the protein $Ca_v1.2$ $\alpha1_C$-subunit have been reduced, whereas $K_{Ca}1.1$ channel activity was normalized in these mesenteric vessels [71, 72]. Exercise-induced high shear stress can lead to adaptation in vascular smooth muscle cells (VSMs), which includes alteration of Ca^{2+} concentration and distribution to modulate the contractility status of VSMs. A recent study revealed that physical activity can modulate L-type voltage-gated Ca^{2+} channels in smooth muscle cells by inducing calcium-dependent protein kinase C (PKC) signalling as a response to enhanced shear stress and cyclic stretch [73]. These significant adaptive effects of exercise are supported by another study which confirmed the activation of different ion channels including voltage-gated L-type Ca^{2+} channel ($Ca_v1.2$), large conductance Ca^{2+}-activated K^+ channel (BK_{Ca}), and voltage-gated K^+ channel (K_v)[74]. Furthermore, a crucial role of Piezo 1 channel in sensing physical exercise and causing vasoconstriction due to high-shear stress has been confirmed by a study by Rode et al., who revealed that physical activity performance is suppressed because of

inhibition of the Piezo 1 channel in endothelial cells [75].

In clinical studies, improved systolic and diastolic function has been linked to exercise-trained individuals [76, 77] whereas animal model studies declared a beneficial effect of endurance exercise on enhancing cardiac contraction-relaxation velocities and force generation [78, 79]. Exercise can lead to improved coupling efficiency between activation of subsarcolemmal ryanodine receptors (RyR) and L-type Ca^{2+} channel-mediated Ca^{2+} entry, the effect which can result in alteration in intracellular concentration of Ca^{2+}. Additionally, physical activity can enhance the expression and efficiency of sodium-calcium exchanger and sarcoendoplasmic reticulum Ca^{2+} ATPase [79, 80]. Another study found that increased sensitivity of cardiomyocytes' contractile system to calcium can be ameliorated by exercise due to, at least partly, increased expression of Na^+/H^+ antiporter and changed regulation of intracellular pH [81].

In the case of pathological cardiac remodelling, a lack of upregulation of cardiac ion channels relative to myocyte hypertrophy causes electrical instability in the heart [82]. In contrast, the upregulation of depolarizing and repolarizing currents can happen in physiological hypertrophy, which is considered protection against abnormal electrical signalling in the exercised heart [83, 84]. Swim training for 4 weeks caused augmentation of outward K^+ current densities (for example, $I_{to,f}$, I_K, slow, I_{ss}, and I_{K1}) and elevated expression of both molecular component and total protein levels of Kv and Kir subunits [84]. Interestingly, electrocardiographic parameters, including QT intervals and ventricular waveforms in swim-trained animals were similar to controls, demonstrating maintained electrical function. Furthermore, the same group of authors found that swim training of mice led to a rise in the expression of the K^+ channel subunit, the effect which happens independently of cellular hypertrophy and Akt1 signalling [85]. In contrast, other convincing results revealed that vigorous endurance exercise could have a deleterious effect on heart function because middle-aged endurance athletes have a higher prevalence of AF [86, 87]. Therefore, further prospective cohort studies are required to thoroughly examine this variation in results and deduce the extent of exercise, which has only a beneficial cardiovascular impact.

Effect of Exercise on Blood Volume and Components

The principal role of red blood cells (RBC) is to carry oxygen from the lungs and deliver it to the tissues, and to transport waste, e.g., carbon dioxide, back from the tissues to the lungs. Researchers have found that trained athletes have a reduced mean age of the circulating RBC. However, enhanced oxygen release and deformability have been noticed in the younger RBCs, which explains the ameliorated tissue oxygen supply during exercise [88]. The function of erythrocytes, leucocytes, and platelets is improved after three months of running exercise for sedentary overweight middle-aged men, the effect of which may lead to a decrease in cardiovascular risk [89]. Another follow-up study has studied the effect of short-term (30 min) standard treadmill exercise on blood cells and found that more significant changes were reported in platelet parameters compared with other hematological parameters [90].

Although trained athletes have a higher level of the total mass of RBC and hemoglobin, a low hematocrit value is reported in the trained athletes and this is due to an increased plasma volume. Persuasive evidence is revealed from both cross-sectional and longitudinal studies that blood volume is changed due to regular physical activity and this change is mainly due to the expansion or contraction of plasma volume, especially on the first days of physical activity [91]. The exercise-induced blood volume is beneficial for many crucial functions including more blood volume for heart filling, stroke volume, and cardiovascular stability as well as more body fluid for heat dissipation, and thermoregulation during exercise [92].

Another recent study has investigated the impact of six weeks of sprint-interval training on maximal oxygen uptake and central hemodynamic factors showed a significant elevation in hemoglobin mass, blood volume, and cardiac output in exercised subjects. Therefore, the authors suggested that the central hemodynamic adaptations are associated with a marked improvement in maximal oxygen uptake during physical training [93]. The same authors studied the impact of the same pattern of physical activity on maximal cardiac output and maximal oxygen consumption, as well as the relative importance of hypervolemic responses to them. They found that the hypervolemic response has a critical role in increases in maximal oxygen consumption following physical activity [94]. However, it seems that plasma volume expansion is independent of the volume of intervals of exercise, as the expansion of plasma volume was similar after four, six, and eight intervals of cycle ergometry [95]. Table 1 summarises the effects of regular physical activity on the cardiovascular system.

TYPE OF HEALTHY EXERCISE PROGRAM

Although many exercise programs were studied and suggested to get a better positive outcome in cardiovascular health, the program of 30 minutes of continuous modest exercise for at least three, preferably all, days of the week is considered the optimum in meeting the benefits and reducing the cardiovascular events [96]. This kind of exercise and benefits can be gained by fast walking at a rate of 3–4 miles/hour, cycling, and swimming. However, other reports demonstrated that intermittent shorter bouts, for 10 minutes, of daily activities of moderate intensity can afford the same cardiovascular benefits [97] especially if the total accumulated duration reaches 30 min/day. Additionally, it has been found that even very short periods (~2 min/hour) of light-intensity exercise can grant an advantage over a sedentary lifestyle [98]. In contrast, the transition from moderately active to very active improved cardiovascular health less than going from the lowest fitness level to the mild level. [96]. Figure 1 summarises the physiological adaptations of regular exercise.

Figure 1. Summary of physiological adaptations after regular exercise. CV = Cardiovascular.

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Table 1. The effects of regular physical activity on the cardiovascular system.

Effect of physical activity on the cardiovascular system	Reference
Decreasing cardiovascular risk factors	[13, 14]
Antihyperlipidemic effect	[17, 57]
Enhancing physiological angiogenesis	[22, 23]
Enhancing antioxidant status	[31, 32]
Augmentation of oxidative stress (high intensity exercise)	[33, 35]
Increasing vascular expression of nitric oxide synthase	[40]
Reducing endothelial angiotensin II type 1 receptor expression	[41]
Reducing the pathological process of vascular remodelling	[42]
Decreasing circulating levels of endothelin-1	[42]
Improving balance between prostacyclin and thromboxane levels	[43]
Increasing peak reactive hyperemic blood flow	[45]
Inducing arterial enlargement	[46]
Decreasing the resting heart rate	[49, 50]
Antihypertensive effect	[37, 53]
Inhibition of coronary artery atherosclerosis	[61, 62]
Inhibition of carotid artery atherosclerosis	[65]
Reducing the expression of protein Cav1.2 α1C-subunit	[71]
Modulating L-type voltage-gated Ca^{2+} channels	[73]
Improving systolic and diastolic function	[76, 77]
Enhancing expression of Na-Ca exchanger and sarcoendoplasmic reticulum Ca^{2+} ATPase	[79, 80]
Increasing expression of Na^{+}/H^{+} antiporter	[81]
Augmentation of outward K^{+} current densities	[84]
Inducing atrial fibrillation (vigorous endurance exercise)	[86, 87]
Improving red blood cells, white blood cells, and platelets functions	[89]
Modulating blood volume	[91, 92]

CONCLUSION

Exercise profoundly impacts cardiovascular functions, including those beyond expected from exercise-induced modifications of traditional cardiovascular risk factors. According to the evidence presented in this review, regular exercise has other primary impacts on different cardiovascular aspects, such as angiogenesis, oxidative stress, vascular tone, heart rate, BP, electrical action potential, and blood volume and its components. Despite this evidence, it is still unknown to what extent the salutary adaptations in the cardiovascular system contribute to the advantages of physical activity in preventing cardiovascular diseases. There are still gaps in knowledge regarding the extent, duration, and type of physical activity that is optimum for getting each of the physiological benefits mentioned in this review. Collectively, more studies are recommended to declare the cellular/molecular consequences of exercise-induced adaptations in both physiological conditions and even in different cardiovascular diseases. It is highly recommended to encourage people to engage in regular exercise as a preventive and therapeutic modality against various cardiovascular diseases. However, for selected patients with cardiovascular diseases, exercise testing is crucial before engaging in vigorous exercise.

ETHICAL DECLARATIONS

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Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable (no individual personal data included).

Availability of Data and Material

Not applicable.

Competing Interests

The author declares that there is no conflict of interest.

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Authors' Contributions

The author contributed to the whole work. The author read and approved the final version of the study.

REFERENCES

[1] K. Dhuli *et al.* Physical activity for health. *Journal of preventive medicine and hygiene*, 63(2):150–159, 2022.

[2] B. Y. Kim, D. H. Choi, C. H. Jung, S. K. Kang, J. O. Mok, and C. H. Kim. Obesity and physical activity. *Journal of Obesity and Metabolic Syndrome*, 26(1):15–22, 2017.

[3] G. Samuelson. Global strategy on diet, physical activity and health. *Scandinavian Journal of Nutrition/Naringsforskning*, 48(2):57, 2004.

[4] S. Jones *et al.* Improved exercise-related skeletal muscle oxygen consumption following uptake of endurance training measured using near-infrared spectroscopy. *Frontiers in Physiology*, 8(DEC), 2017.

[5] H. Wang, Y. Huang, and Y. Zhao. Efficacy of Exercise on Muscle Function and Physical Performance in Older Adults with Sarcopenia: An Updated Systematic Review and Meta-Analysis. *International Journal of Environmental Research and Public Health*, 19(13), 2022.

[6] G. Distefano and B. H. Goodpaster. Effects of exercise and aging on skeletal muscle. *Cold Spring Harbor Perspectives in Medicine*, 8(3), 2018.

[7] X. Chang, S. Xu, and H. Zhang. Regulation of bone health through physical exercise: Mechanisms and types. *Frontiers in Endocrinology*, 13, 2022.

[8] T. E. Howe *et al.* Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database of Systematic Reviews*, 2011.

[9] M. G. Benedetti, G. Furlini, A. Zati, and G. L. Mauro. The Effectiveness of Physical Exercise on Bone Density in Osteoporotic Patients. *BioMed Research International*, 2018, 2018.

[10] S. Legey *et al.* Relationship Among Physical Activity Level, Mood and Anxiety States and Quality of Life in Physical Education Students. *Clinical Practice & Epidemiology in Mental Health*, 13(1):82–91, 2017.

[11] L. T. Pham, R. Hernandez, D. Spruijt-Metz, J. S. Gonzalez, and E. A. Pyatak. Movement matters: short-term impacts of physical activity on mood and well-being. *Journal of Behavioral Medicine*, 46(5):781–790, 2023.

[12] M. Pearce *et al.* Association between Physical Activity and Risk of Depression: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, 79(6):550–559, 2022.

[13] K. Pinckard, K. K. Baskin, and K. I. Stanford. Effects of Exercise to Improve Cardiovascular Health. *Frontiers in Cardiovascular Medicine*, 6, 2019.

[14] E. Carpio-Rivera, J. Moncada-Jiménez, W. Salazar-Rojas, and A. Solera-Herrera. Acute effects of exercise on blood pressure: A meta-analytic investigation. *Arquivos Brasileiros de Cardiologia*, 106(5):422–433, 2016.

[15] B. Jabbarzadeh Ganjeh *et al.* Effects of aerobic exercise on blood pressure in patients with hypertension: a systematic review and dose-response meta-analysis of randomized trials. *Hypertension Research*, 47(2):385–398, 2024.

[16] T. R. Ramis *et al.* Effects of exercise modalities on decreased blood pressure in patients with hypertension. *Frontiers in Physiology*, 13, 2022.

[17] E. J. Rhee *et al.* 2018 Guidelines for the Management of Dyslipidemia. *Korean Journal of Internal Medicine*, 34(4):723–771, 2019.

[18] A. Muscella, E. Stefàno, and S. Marsigliante. The effects of exercise training on lipid metabolism and coronary heart disease. *American Journal of Physiology - Heart and Circulatory Physiology*, 319(1):H76–H88, 2020.

[19] K. A. Varady, A. C. St-Pierre, B. Lamarche, and P. Jones H. Jones. Effect of plant sterols and endurance training on LDL particle size and distribution in previously sedentary hypercholesterolemic adults. *European Journal of Clinical Nutrition*, 59(4):518–525, 2005.

[20] K. Krüger, P. Tirekoglou, and C. Weyh. Immunological mechanisms of exercise therapy in dyslipidemia. *Frontiers in Physiology*, 13, 2022.

[21] M. Ross, C. K. Kargl, R. Ferguson, T. P. Gavin, and Y. Hellsten. Exercise-induced skeletal muscle angiogenesis: impact of age, sex, angiocrines and cellular mediators. *European Journal of Applied Physiology*, 123(7):1415–1432, 2023.

[22] A. Tryfonos *et al.* Exercise training enhances angiogenesis-related gene responses in skeletal muscle of patients with chronic heart failure. *Cells*, 10(8), 2021.

[23] B. X. Song *et al.* The effect of exercise on blood concentrations of angiogenesis markers in older adults: A systematic review and meta-analysis. *Neurobiology of Aging*, 135:15–25, 2024.

[24] H. S. Yeo and J. Y. Lim. Effects of different types of exercise training on angiogenic responses in the left ventricular muscle of aged rats. *Experimental Gerontology*, 158, 2022.

[25] D. J. Duncker and R. J. Bache. Regulation of coronary blood flow during exercise. *Physiological Reviews*, 88(3):1009–1086, 2008.

[26] N. Sylviana, H. Goenawan, Y. Susanti, R. Lesmana, I. Megantara, and Setiawan. Effect of different intensities aerobic exercise to cardiac angiogenesis regulation on Wistar rats. *Polish Journal of Veterinary Sciences*, 25(1):119–128, 2022.

[27] Y. Bei *et al.* Lymphangiogenesis contributes to exercise-induced physiological cardiac growth. *Journal of Sport and Health Science*, 11(4):466–478, 2022.

[28] H. Chen *et al.* Exercise training maintains cardiovascular health: signaling pathways involved and potential therapeutics. *Signal Transduction and Targeted Therapy*, 7(1), 2022.

[29] G. Pizzino *et al.* Oxidative Stress: Harms and Benefits for Human Health. *Oxidative Medicine and Cellular Longevity*, 2017, 2017.

[30] J. Angulo, M. El Assar, A. Álvarez-Bustos, and L. Rodríguez-Mañas. Physical activity and exercise: Strategies to manage frailty. *Redox Biology*, 35, 2020.

[31] M. Bernardi and I. Peluso. Interactions between oxidative stress and cardiorespiratory fitness: Old and new biomarkers. *Current Opinion in Toxicology*, 20-21:15–22, 2020.

[32] A. de F. Brito, C. V. C. de Oliveira, G. A. Cardoso, J. M. S. de Lucena, J. di P. dos S. Sousa, and A. A. de Souza. Oxidative Stress and Vascular Diseases: Effect of Physical Exercise. In *Free Radicals, Antioxidants and Diseases*, pages 25–48. 2018.

[33] A. I. Galán *et al.* Exercise, oxidative stress and risk of cardiovascular disease in the elderly. Protective role of

http://doi.org/10.33091/amj.2024.150002.1729

antioxidant functional foods. *BioFactors*, 27(1-4):167–183, 2006.

[34] G. A. Ribeiro-Samora *et al.* Inflammation and oxidative stress in heart failure: Effects of exercise intensity and duration. *Brazilian Journal of Medical and Biological Research*, 50(9), 2017.

[35] A. Shibata *et al.* Increased oxidative stress during exercise predicts poor prognosis in patients with acute decompensated heart failure. *ESC Heart Failure*, 8(5):3885–3893, 2021.

[36] T. Tofas, D. Draganidis, C. K. Deli, K. Georgakouli, I. G. Fatouros, and A. Z. Jamurtas. Exercise-induced regulation of redox status in cardiovascular diseases: The role of exercise training and detraining. *Antioxidants*, 9(1), 2020.

[37] Y. Song *et al.* The Molecular Mechanism of Aerobic Exercise Improving Vascular Remodeling in Hypertension. *Frontiers in Physiology*, 13, 2022.

[38] D. J. Green, N. T. Cable, C. Fox, J. M. Rankin, and R. R. Taylor. Modification of forearm resistance vessels by exercise training in young men. *Journal of Applied Physiology*, 77(4):1829–1833, 1994.

[39] D. H. J. Thijssen, A. J. Maiorana, G. O'Driscoll, N. T. Cable, M. T. E. Hopman, and D. J. Green. Impact of inactivity and exercise on the vasculature in humans. *European Journal of Applied Physiology*, 108(5):845–875, 2010.

[40] M. Garcia, S. Cabral, C. Rodriguez, D. Conde, and A. N. Gurovich. Exercise-Induced Shear Stress Upregulates eNOS Protein in vitro . *The FASEB Journal*, 36(S1), 2022.

[41] B. Ramkhelawon *et al.* Shear stress regulates angiotensin type 1 receptor expression in endothelial cells. *Circulation Research*, 105(9):869–875, 2009.

[42] C. M. McEniery, I. B. Wilkinson, D. G. Jenkins, and D. J. Webb. Endogenous endothelin-1 limits exercise-induced vasodilation in hypertensive humans. *Hypertension*, 40(2):202–206, 2002.

[43] A. H. Hansen, M. Nyberg, J. Bangsbo, B. Saltin, and Y. Hellsten. Exercise training alters the balance between vasoactive compounds in skeletal muscle of individuals with essential hypertension. *Hypertension*, 58(5):943–949, 2011.

[44] C. Goto *et al.* Effect of different intensities of exercise on endothelium-dependent vasodilation in humans: Role of endothelium-dependent nitric oxide and oxidative stress. *Circulation*, 108(5):530–535, 2003.

[45] M. J. Joyner and D. P. Casey. Regulation of increased blood flow (Hyperemia) to muscles during exercise: A hierarchy of competing physiological needs. *Physiological Reviews*, 95(2):549–601, 2015.

[46] A. L. Spence, H. H. Carter, L. H. Naylor, and D. J. Green. A prospective randomized longitudinal study involving 6 months of endurance or resistance exercise. Conduit artery adaptation in humans. *Journal of Physiology*, 591(5):1265–1275, 2013.

[47] D. H. J. Thijssen *et al.* Time course of arterial remodelling in diameter and wall thickness above and below the lesion after a spinal cord injury. *European Journal of Applied Physiology*, 112(12):4103–4109, 2012.

[48] D. H. J. Thijssen, R. R. Scholten, I. C. L. Van Den Munckhof, N. Benda, D. J. Green, and M. T. E. Hopman. Acute change in vascular tone alters intima-media thickness. *Hypertension*, 58(2):240–246, 2011.

[49] S. Bahrainy, W. C. Levy, J. M. Busey, J. H. Caldwell, and J. R. Stratton. Exercise training bradycardia is largely explained by reduced intrinsic heart rate. *International Journal of Cardiology*, 222:213–216, 2016.

[50] A. K. Reimers, G. Knapp, and C. D. Reimers. Effects of exercise on the resting heart rate: A systematic review and meta-analysis of interventional studies. *Journal of Clinical Medicine*, 7(12), 2018.

[51] B. Morseth *et al.* Physical activity, resting heart rate, and atrial fibrillation: The Tromsø Study. *European Heart Journal*, 37(29):2307–2313, 2016.

[52] L. Zhang *et al.* Inhibition of endothelial nitric oxide synthase reverses the effect of exercise on improving cognitive function in hypertensive rats article. *Hypertension Research*, 41(6):414–425, 2018.

[53] Y. Higashi. Exercise is a double-edged sword for endothelial function. *Hypertension Research*, 39(2):61–63, 2016.

[54] A. D. Vikulov, E. Yu Drattsev, A. A. Mel'nikov, and V. V. Alekhin. Vascular tone and regular physical exercise. *Human Physiology*, 35(5):636–641, 2009.

[55] D. T. Beck, J. S. Martin, D. P. Casey, and R. W. Braith. Exercise training improves endothelial function in resistance arteries of young prehypertensives. *Journal of Human Hypertension*, 28(5):303–309, 2014.

[56] C. De Ciuceis, D. Rizzoni, and P. Palatini. Microcirculation and Physical Exercise in Hypertension. *Hypertension*, 80(4):730–739, 2023.

[57] Y. A. Kesaniemi, Jr Danforth E., M. D. Jensen, P. G. Kopelman, P. Lefebvre, and B. A. Reeder. Dose-response issues concerning physical activity and health: An evidence-based symposium. In *Medicine and Science in Sports and Exercise*, pages S351–S358, 2001.

[58] A. S. Leon and O. A. Sanchez. Response of blood lipids to exercise training alone or combined with dietary intervention. In *Medicine and Science in Sports and Exercise*, pages S502–S515, 2001.

[59] C. Wharton and J. K. Nustad. Effects of the amount and intensity of exercise on plasma lipoproteins: Editor's comments. *American Journal of Health Promotion*, 20(4):300, 2006.

[60] M. A. Sarzynski *et al.* Effects of Increasing Exercise Intensity and Dose on Multiple Measures of HDL (High-Density Lipoprotein) Function. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 38(4):943–952, 2018.

[61] P. T. Williams. Physical fitness and activity as separate heart disease risk factors: A meta-analysis. *Medicine and Science in Sports and Exercise*, 33(5):754–761, 2001.

[62] M. Kwaśniewska *et al.* Long-term effect of different physical activity levels on subclinical atherosclerosis in middle-aged men: A 25-year prospective study. *PLoS ONE*, 9(1):e85209, 2014.

[63] M. Pynn, K. Schäfer, S. Konstantinides, and M. Halle. Exercise Training Reduces Neointimal Growth and Stabilizes Vascular Lesions Developing after Injury in Apolipoprotein E-Deficient Mice. *Circulation*, 109(3):386–392, 2004.

[64] U. Laufs *et al.* Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 25(4):809–814, 2005.

[65] L. Chen *et al.* Physical activity and carotid atherosclerosis risk reduction in population with high risk for cardiovascular diseases: a cross-sectional study. *BMC Public Health*, 22(1), 2022.

[66] Á. Herraiz-Adillo *et al.* Physical fitness in male adolescents and atherosclerosis in middle age: a population-based cohort study. *British Journal of Sports Medicine*, 58(8):411–420, 2024.

[67] R. De Bosscher *et al.* Lifelong endurance exercise and its relation with coronary atherosclerosis. *European Heart Journal*, 44(26):2388–2399, 2023.

[68] V. L. Aengevaeren *et al.* Exercise and Coronary Atherosclerosis: Observations, Explanations, Relevance, and Clinical Management. *Circulation*, pages 1338–1350, 2020.

[69] P. D. Thompson. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 23(8):1319–1321, 2003.

[70] J. H. A. Folgering, R. Sharif-Naeini, A. Dedman, A. Patel, P. Delmas, and E. Honoré. Molecular basis of the mammalian pressure-sensitive ion channels: Focus on vascular mechanotransduction. *Progress in Biophysics and Molecular Biology*, 97(2-3):180–195, 2008.

[71] Y. Chen, H. Zhang, Y. Zhang, N. Lu, L. Zhang, and L. Shi. Exercise intensity-dependent reverse and adverse remodeling of voltage-gated Ca 2+ channels in mesenteric arteries from spontaneously hypertensive rats. *Hypertension Research*, 38(10):656–665, 2015.

[72] L. Shi *et al.* Chronic exercise normalizes changes in Ca v1.2 and KCa 1.1 channels in mesenteric arteries from spontaneously hypertensive rats. *British Journal of Pharmacology*, 172(7):1846–1858, 2015.

[73] J. Hong and Y. Park. Microvascular function and exercise training: Functional implication of nitric oxide signaling and ion channels. *Pulse*, 12(1):27–33, 2024.

[74] E. A. Mokelke, M. Alloosh, and M. Sturek. Specificity of Ca2 +-activated K+ channel modulation in atherosclerosis and aerobic exercise training. In *Current Topics in Membranes*, volume 90, pages 123–139. 2022.

[75] B. Rode *et al.* Piezo1 channels sense whole body physical activity to reset cardiovascular homeostasis and enhance performance. *Nature Communications*, 8(1), 2017.

[76] S. Ferguson, N. Gledhill, V. K. Jamnik, C. Wiebe, and N. Payne. Cardiac performance in endurance-trained and moderately active young women. *Medicine and Science in Sports and Exercise*, 33(7):1114–1119, 2001.

[77] B. T. A. Esch, J. M. Scott, M. J. Haykowsky, D. C. McKenzie, and D. E. R. Warburton. Diastolic ventricular interactions in endurance-trained athletes during orthostatic stress. *American Journal of Physiology - Heart and Circulatory Physiology*, 293(1), 2007.

[78] G. M. Diffee and E. Chung. Altered single cell force-velocity and power properties in exercise-trained rat myocardium. *Journal of Applied Physiology*, 94(5):1941–1948, 2003.

[79] O. J. Kemi, O. Ellingsen, G. L. Smith, and U. Wisloff. Exercise-induced changes in calcium handling in left ventricular cardiomyocytes. *Frontiers in Bioscience*, 13(1):356–368, 2008.

[80] O. J. Kemi and U. Wisløff. Mechanisms of exercise-induced improvements in the contractile apparatus of the mammalian myocardium. *Acta Physiologica*, 199(4):425–439, 2010.

[81] U. Wisløff *et al.* Increased contractility and calcium sensitivity in cardiac myocytes isolated from endurance trained rats. *Cardiovascular Research*, 50(3):495–508, 2001.

[82] C. Marionneau, S. Brunet, T. P. Flagg, T. K. Pilgram, S. Demolombe, and J. M. Nerbonne. Distinct cellular and molecular mechanisms underlie functional remodeling of repolarizing K+ currents with left ventricular hypertrophy. *Circulation Research*, 102(11):1406–1415, 2008.

[83] A. Biffi *et al.* Relation Between Training-Induced Left Ventricular Hypertrophy and Risk for Ventricular Tachyarrhythmias in Elite Athletes. *American Journal of Cardiology*, 101(12):1792–1795, 2008.

[84] K. C. Yang, N. C. Foeger, C. Marionneau, P. Y. Jay, J. R. McMullen, and J. M. Nerbonne. Homeostatic regulation of electrical excitability in physiological cardiac hypertrophy. *Journal of Physiology*, 588(24):5015–5032, 2010.

[85] K. C. Yang, Y. T. Tseng, and J. M. Nerbonne. Exercise training and PI3Kα-induced electrical remodeling is independent of cellular hypertrophy and Akt signaling. *Journal of Molecular and Cellular Cardiology*, 53(4):532–541, 2012.

[86] J. Abdulla and J. R. Nielsen. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Europace*, 11(9):1156–1159, 2009.

[87] N. Drca, A. Wolk, M. Jensen-Urstad, and S. C. Larsson. Atrial fibrillation is associated with different levels of physical activity levels at different ages in men. *Heart*, 100(13):1037–1042, 2014.

[88] H. Mairbäurl. Red blood cells in sports: Effects of exercise and training on oxygen supply by red blood cells. *Frontiers in Physiology*, 4, 2013.

[89] M. Jafari. Effect of Running Training on White Blood Cells and Platelets Count and Red Blood Cells Distribution Width in Untrained Middle-Aged Men. *International Journal of Sport Studies for Health*, 2(1):33–36, 2019.

[90] O. Chizoba O, M. Emmanuel I, A. Christopher O, and A. Kenneth U. Changes in white blood cell, red blood cell and platelet parameters following short term aerobic exercise in students of Nnamdi Azikiwe University, Nigeria. *International Journal of Sport, Exercise and Health Research*, 4(2):73–78, 2020.

[91] M. N. Sawka, V. A. Convertino, E. R. Eichner, S. M. Schnieder, and A. J. Young. Blood volume: Importance and adaptations to exercise training, environmental stresses, and trauma/sickness. *Medicine and Science in Sports and Exercise*, 32(2):332–348, 2000.

[92] V. A. Convertino. Blood volume response to physical activity and inactivity. *American Journal of the Medical Sciences*, 334(1):72–79, 2007.

[93] M. Mandić *et al.* Improvements in Maximal Oxygen Uptake After Sprint-Interval Training Coincide with Increases in Central Hemodynamic Factors. *Medicine and Science in Sports and Exercise*, 54(6):944–952, 2022.

[94] M. Mandić *et al.* Increased maximal oxygen uptake after sprint-interval training is mediated by central haemodynamic factors as determined by right heart catheterization. *Journal of Physiology*, 601(12):2359–2370, 2023.

[95] W. B. Nelson *et al.* The influence of exercise volume and posture on exercise-induced plasma volume expansion. *Physiological Reports*, 11(4), 2023.

[96] J. Myers *et al.* Exercise Capacity and Mortality among Men Referred for Exercise Testing. *New England Journal of Medicine*, 346(11):793–801, 2002.

http://doi.org/10.33091/amj.2024.150002.1729

[97] M. N. Ahmadi *et al.* Brief bouts of device-measured intermittent lifestyle physical activity and its association with major adverse cardiovascular events and mortality in people who do not exercise: a prospective cohort study. *The Lancet Public Health*, 8(10):e800–e810, 2023.

[98] S. Beddhu, G. Wei, R. L. Marcus, M. Chonchol, and T. Greene. Light-intensity physical activities and mortality in the United States general population and CKD subpopulation. *Clinical Journal of the American Society of Nephrology*, 10(7):1145–1153, 2015.