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Cardiorespiratory Fitness and Atherosclerosis: Recent Data and Future Directions

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Abstract

Historically the relationship between exercise and the cardiovascular system was viewed as unidirectional, with disease resulting in exercise limitation and hazard. This article reviews and explores the bidirectional nature, delineating the effects, generally positive, on the cardiovascular system and atherosclerosis. Exercise augments eNOS, affects redox potential, and favorably affects mediators of atherosclerosis including lipids, glucose homeostasis, and inflammation. There are direct effects on the vasculature as well as indirect benefits related to exercises induced changes in body composition and skeletal muscle. Application of aerobic exercise to specific populations is described, with the hope that this knowledge will move the science forward and improve individual patient outcome.

Keywords

Exercise; Cardiorespiratory Fitness; Cardiac Rehabilitation; eNOS; Cardiovascular disease prevention

Introduction

Historically, the relationship between atherosclerotic cardiovascular disease was thought to be unidirectional, wherein myocardial ischemia and/or prior myocardial infarction limited cardiac output, and thereby impaired an individual's exercise capacity. A wide variety of more recent data suggests that this relationship is bidirectional, with regular exercise producing salutary effects on the atherosclerotic process and its clinical manifestations. This

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Compliance with Ethics Guidelines

Conflict of Interest

Emile Mehanna, Anne Hamik, and Richard A Josephson declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

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review will summarize the mechanisms and evidence for exercise effects on atherosclerosis, from the molecular, to the individual, to the epidemiologic, and how this knowledge can be directly applied to the benefit of patients.

Regular exercise has been thought to be healthful, certainly from the time of Hippocrates, though this benefit was generally conceived as producing primordial prevention, or inhibiting the development of atherosclerotic and other cardiovascular diseases. Secondary prevention, or the prevention of clinical events in those with established atherosclerosis was controversial, with many alleging that any possible benefit was over shadowed by the risk of myocardial infarction or death. Up until the latter part of the twentieth century, secondary prevention typically consisted of a variety of measures such as medication and tobacco cessation but not structured exercise. Bed rest after myocardial infarction was the norm, and exercise thought to be unacceptably dangerous. Fortunately, there is now a consensus that exercise is indeed favorable across the prevention continuum (primordial, primary, and secondary) of patients with atherosclerotic disease, and we shall describe the evidence that supports this benefit, even in those with severe manifestations of the sequelae of atherosclerosis.

Cardiorespiratory Fitness

Exercise has broadly been defined as a planned, structured, repetitive, and purposeful physical activity aiming at the improvement or maintenance of physical fitness, which by itself includes cardiorespiratory fitness, muscle strength, body composition and flexibility. The assessment of cardiorespiratory fitness has best been done by measuring the maximal (or peak) oxygen uptake (VO_2). Many studies estimate fitness levels by measurement of either the peak work rate or MET level (where 1 MET = an energy expenditure of $14.6 \text{ kJ} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} = 3.5 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) achieved during graded exercise tests [1]. The cardiovascular system's adaptation to exercise is driven by the type, dose and intensity of exercise. The two recognized types of exercise are dynamic and isometric. Dynamic exercise results in contraction of muscles with movement of one or more joints while isometric exercise involves sustained muscle contraction with no change in length of the involved muscle group or joint motion. Cardiorespiratory fitness is improved by aerobic exercise, which falls in the dynamic category. Training results in improvement in cardiac efficiency and decrease myocardial oxygen demand [2]. During exercise, coronary blood flow increases to match the increased demand. This mechanism depends on vasodilatation of coronary arterioles, a process that can be limited by the presence of coronary artery disease. This is likely due to the dysfunctional endothelium being unable to produce endothelium-derived factors to cause adequate coronary vasodilatation and/or a significant reduction in perfusion pressure distal to a significant coronary artery stenosis [3, 4]. There appears to be a beneficial effect of exercise training (ET) on arterial endothelial function, attenuation of acetylcholine-driven vasoconstriction, increased nitric oxide production and sensitization of the microvasculature to adenosine-mediated vasodilatation [5].

A surrogate marker for myocardial work is the rate pressure product (RPP), which is defined by the systolic blood pressure (SBP) multiplied by the heart rate (HR). ET and conditioning leads to increase in basal parasympathetic tone and lowering of catecholamines, which

reduces HR at rest and during submaximal exercise [6]. This allows longer diastolic time in each cardiac cycle and a longer time for coronary perfusion. ET also has favorable effects on blood pressure which will be discussed in a later section.

Thus, the proximate result of exercise therapy is to improve the function of the heart and the peripheral tissues. Improved organ function relies heavily upon optimized metabolism. Oxidative stress, or the imbalance between production and detoxification of reactive oxygen species (ROS) that are the chemical byproducts of metabolism, occurs when functional demands upon a tissue increase. Data that supports beneficial hemodynamic and molecular changes in cardiovascular/skeletal muscle metabolism exist in particular for regular, aerobic (dynamic) exercise of moderate-to-high intensity. In fact, mild oxidative stress from moderate exercise stimulates antioxidant signaling pathways, resulting in physiological adaptation [7]. In the myocardium, the strongest evidence supporting an exercise-metabolic mechanism of enhanced function is the upregulation of the antioxidant manganese superoxide dismutase (MnSOD) that occurs resultant to exercise [8]. Roles for exercise-induced increases in cardiac heat shock proteins and other mechanisms that aid in regulation of intracellular calcium concentration and a mitochondrial phenotype that protect against ROS and even cardiomyocyte apoptosis are highly likely, but as yet have not been well demonstrated in human exercise physiology studies.

Benefits of exercise to skeletal muscle physiology include enhanced metabolic substrate delivery, substrate utilization by mitochondria, and myocyte contractility. These beneficial adaptations are readily identified by increased V_{O2} max after exercise training [1, 9]. Review of the numerous positive adaptations to exercise by skeletal muscle is beyond the scope of this article and has recently been elegantly summarized elsewhere [10]. Briefly, responses range from epigenetic changes and thus differential gene expression, to altered protein stability and mitochondrial biogenesis, to remodeling of muscle fibers and plasticity in muscle fiber type. A central consequence of these changes is enhancement of glucose utilization by both acute and regular exercise. Skeletal muscle comprises approximately 40% of body mass, has the greatest dynamic range of any tissue in both metabolic rate and blood flow (~20- and 30-fold respectively), and is responsible for ~80% of insulin-mediated glucose utilization [11]. Thus, the potential for skeletal muscle-mediated systemic metabolic effects of exercise is substantial. In fact, a significant mechanism by which exercise training reduces cardiometabolic risk is through increased insulin sensitivity, a concept reinforced by recent data demonstrating that supervised exercise training reduces oxidative stress and cardiometabolic risk in adults with type 2 diabetes [12].

Interestingly, the benefit from exercise-induced improvements in insulin sensitivity may not be restricted to skeletal muscle physiology; endothelial insulin resistance is an independent risk factor for cardiovascular mortality, myocardial infarction, and stroke and may be modifiable by exercise [13]. As an integral component of the microvasculature of both the coronary and peripheral circulations, endothelial cells have a favored status as the primary regulator of tissue perfusion. Signaling pathways converge upon bioavailability of nitric oxide (NO) as the molecular signature of a healthy endothelium and this relates to the balance of oxidant and antioxidant activities [14]. Reduced NO levels are the sine qua non of “dysfunctional” endothelial cells (ECs) seen in atherosclerosis, hypertension, heart failure,

diabetes, and aging [15]. Exercise-induced improvement in endothelial function is seen in both healthy young [15] and elderly patients [16], as demonstrated by flow-mediated dilatation (FMD), the technique used to measure shear stress-induced NO.

Of note, exercise-induced NO bioavailability appears blunted in patients with diabetes [17] and greatest early in a bout of a low-to-moderate intensity exercise [18]. These interesting observations may correspond to differential basal and exercise-modified levels of vascular oxidative stress. High-intensity exercise can cause transient endothelial dysfunction, followed by enhanced NO bioavailability a few hours later [19, 20]. This dynamic is thought to be secondary to the effects of increased shear stress (the mechanical force of flowing blood exerted onto and parallel to the vascular wall) from high intensity exercise acutely overwhelming the antioxidant capabilities of the endothelium, with a subsequent phase of enhanced antioxidant activity [21]. Indeed, shear stress is a potent upregulator of endothelial NO synthase (eNOS) and also decreases NO inactivation by increasing the levels of the antioxidant superoxide dismutase (SOD). SOD counteracts the NO-scavenging effects of the primary oxidizing force in the vascular wall, NADPH oxidase [22, 23]. The vascular remodeling that occurs with chronic exercise – increased luminal diameter with a higher luminal:wall thickness ratio – appears to be a response to recurrent exposure to increased shear stress. An increased lumen diameter results in normalization of shear stress, and this likely explains the reduction in enhancement of post-exercise FMD with chronic exercise [14]. Diabetic patients may show a reduced response by FMD due to their increased basal levels of vascular oxidative stress [24].

In addition to control of vasomotor tone (constriction/dilatation) and vascular remodeling, NO has beneficial effects on vascular inflammation, atherogenesis, and thrombosis [25]. Exercise-induced shear stress in combination with a functional endothelium leads to improved supply of metabolic substrates to the myocardium and skeletal muscle. These combined effects of exercise on ECs are postulated as a mechanism for improvements in cardiovascular risk not otherwise explained by traditional risk factors [26]. Strenuous exercise has the potential to overwhelm the antioxidant capabilities of the vasculature as well as lead to muscle injury and subsequent inflammatory activity. As discussed below, current data have not yet allowed determination of a single optimal exercise training regimen (i.e., is moderate or high intensity superior). It is intriguing to consider that individualized basal and exercise-induced ROS activity may provide a molecular signal to allow personalized training prescription [10].

Coronary Heart Disease Risk

Cardiorespiratory fitness is a strong predictor of cardiovascular disease development and all-cause mortality, with increases in cardiorespiratory fitness associated with corresponding decreases in cardiovascular disease risk [27–29]. In a study comparing 786 former Tour de France cyclists with the general French male population, a 41% reduction in mortality was reported [30]. Such beneficial effect of exercise on mortality emanates from both direct [31] and indirect (traditional cardiovascular risk factors modification) impact on atherosclerosis.

Exercise has been linked to alteration in glucose metabolism. Here, as well, the effects of exercise are both direct (catecholamines augment non-insulin dependent glucose uptake by tissues) as well as indirect (increases in muscle mass induced by training augment resting insulin independent glucose utilization, as well as via improvements in body weight, and changing/improved body composition). The reduction in HBA1C was most pronounced when both dynamic and isometric exercise was performed [32, 33]. This translated into reduction in the prevalence of the metabolic syndrome as shown by the Heritage Family study in which 20 weeks of aerobic exercise caused a 32% reduction in the prevalence of the metabolic syndrome (the biochemical mechanism has been described before). This and other data support the recommendations of national organizations advising the combination of dynamic and isometric exercise when feasible to maximize the improvement in glucose control in individuals with type 2 diabetes mellitus [34].

The effects of exercise on lipid levels have been variable, with the most consistent effect being the increase in HDL [35]. Swift et al. summarize the improvement in lipid profiles caused by exercise by a total reduction of 5% for the total cholesterol, 15% reduction for triglycerides, 2% for LDL-C and 5% for the ratio (LDL-C/HDL-C). There was also a 40% reduction in inflammation measured by hs-CRP and an increase in HDL-C of 6% with a greater effect noted in individuals with low baseline HDL-C [36].

Exercise was also been shown to have indirect behavioral effects on tobacco cessation and weight loss. Despite the undisputable direct effect of smoking on atherosclerosis [37, 38], suboptimal successes are still being reported in smoking cessation interventions, with the 12 months abstinence rate remaining less than 20%. Marcus et al. showed in a randomized controlled trial performed on 281 healthy, sedentary female smokers that vigorous exercise facilitated short- and longer-term smoking cessation when combined with a cognitive-behavioral smoking cessation program. Vigorous exercise also improved exercise capacity and delayed weight gain following smoking cessation [39].

Finally, multiple trials and meta-analysis have shown reduction of BP with exercise independent from the type of exercise [40–42]. All these findings led to the incorporation of exercise therapy into the most recent 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk [28].

The Evidence behind Current Practice

Numerous studies of varying size and rigor have examined the role of exercise in altering the outcome of a wide array of maladies including psychiatric disease, neurological or musculoskeletal disease, primary pulmonary disease, and cancer. Pedersen and Saltin recently published an evidence-based review of these studies, along with an attempt to provide disease-specific exercise prescription [43]. Their review highlights the limitations in the quality of data supporting physical activity for several of these chronic diseases despite the volume of publications. In contradistinction, the high level of confidence that physical activity and exercise are of benefit in the prevention and treatment of atherosclerotic cardiovascular disease (CVD) has been codified in widely supported guidelines [44]. Of import, the data that support these guidelines are from observational epidemiological studies

rather than prospective randomized clinical trials that directly test the premise that exercise prevents CVD; for practical reasons (sample size and study duration requirements), such randomized trials are unlikely to be conducted. Thus, much of the recent data is largely represented by studies that focus on specific at-risk populations, investigations of the modification of non-traditional cardiovascular risk factors by exercise, assessment of the relative effectiveness of specific exercise programs in improving surrogate outcomes, and meta-analyses of previous studies. We will focus on some of the more notable studies that reflect these current trends.

Prominent amongst recent studies is the HF-ACTION study, which assessed the efficacy of 12 weeks of supervised training followed by an at-home program in 2,331 patients with systolic heart failure and left ventricular ejection fraction <35% [45]. Over a median follow-up period of 2.5 years, patients receiving exercise training had a lower incidence of cardiovascular mortality and hospital admissions for heart failure. Several sub-group analyses of this study have been published, looking at outcomes in patients with heart failure and diabetes, COPD, cancer, and different gender and ethnicities [46–50]. In general, co-morbidities appeared to reduce the efficacy of exercise therapy while female gender or self-identification as black did not. Thus HF-ACTION supports a broad role for exercise in patients with systolic heart failure, with caveats for those with significant co-morbidities.

Pulmonary arterial hypertension (PAH) confers high morbidity and mortality and is exemplified by an intolerance to exercise. There is a significant need for additional therapies to improve outcomes. The complexity of this disease, including high pulmonary pressures, ventilation-perfusion abnormalities, dysfunction in peripheral oxygen extraction and respiratory muscle dysfunction makes the benefit and safety of exercise therapy difficult to predict. Meta-analysis of studies published between 1980 and 2015 revealed 15 studies of moderate to good quality (using the Downs and Black Quality Index) comprising 477 total patients [51]. Exercise training resulted in significant increase in exercise capacity, modest improvement in VO₂ (1–2ml/kg-min) and functional class, and minimal adverse effects. While the mechanism by which exercise improves these parameters is currently unknown, the safety profile of exercise in PAH patients is of particular import and should encourage better quality, longer-term studies.

Patients with peripheral artery disease (PAD) demonstrate impaired ambulation and limited exercise capacity, poor cardiorespiratory fitness and increased rates of cardiovascular mortality [52]. Also suspected but understudied is a musculoskeletal dysfunction and myopathy that leads to abnormal gait and loss of function [53]. Meta-analyses of the role of exercise in PAD exemplify the difficulty in determining the degree of effect and best mode of exercise therapy for a specific population of patients. Thus, while it is widely accepted that exercise therapy improves walking ability in patients with PAD, a recent review by Parmenter et al. confirmed improvements in 6 minute walking distance and distance to claudication after exercise training (19 aerobic and 5 progressive resistance training programs), but noted very sparse data on performance-based tests of function [54]. Interestingly, patient self-assessment of walking speed, distance, and stair climbing significantly improved after any form of exercise program (home-based, supervised aerobic, or supervised resistance training) [55]; however, systematic review of objective measures of

gait parameters (walking velocity and step length variability) suggest no discernible improvement after either exercise or invasive therapy [56]. Most studies of PAD utilize walking to a predefined level of pain/discomfort as part of the exercise prescription. These results suggest that future studies should include blinding of assessors to subjective measures, formal/objective assessment of muscle strength, performance-based function which predicts activities of daily living performance and disability, and evaluation of alternative exercise regimens for the improvement in these parameters.

With reference to a limited number of primary review articles [57, 58], it is often stated that changes in traditional risk factors (body weight, blood pressure, serum lipids) account for ~60% of the benefit of exercise on CVD, while the role of non-traditional risk factors, in particular the hemodynamic effects of endothelial function (nitric oxide bioavailability) and decreased arterial stiffness, may explain the remainder of the benefit. While this attribution leaves unexplored the role of improved skeletal metabolism (glucose utilization and handling of oxidative stress) on improvement in CVD, it has encouraged the use of measures of arterial stiffness as an indicator of vascular health and a surrogate measure for CVD risk. Indeed, increased vascular stiffness is closely associated with many conditions that increase the risk for adverse cardiovascular events, including aging, atherosclerosis, chronic kidney disease, diabetes, and dyslipidemia [59]. Endurance exercise training in older patients with heart failure and preserved ejection fraction resulted in increased peak VO₂ but no change in endothelial function as determined by brachial artery FMD or arterial stiffness as measured by high resolution carotid artery ultrasound [60]. Exercise training appears less effective in reducing brachial-ankle pulse wave velocity (PWV) in elderly women with hypertension than normotensive elderly women [61]. In younger patients with pre-hypertension, improvements in arterial stiffness parameters were seen only in those patients for whom exercise therapy also lead to significant decreases in resting systolic blood pressure [62]. In patients with type 2 diabetes, aerobic training improved measures of endothelium-independent vasodilation, but not FMD or PWV, two measures designed to assess endothelial-mediated vasoreactivity [63]. A randomized controlled trial of 48 patients with stage 3–4 chronic kidney disease did not show improvement in flow mediated dilation of the brachial artery or carotid-femoral PWV after 3 months of aerobic exercise training, but did demonstrate increase in peak VO₂ [64], while a similarly sized study in patients post renal transplant showed improvement in both parameters [65], indicating the difficulty in extrapolating findings from one patient group to another.

Deriving an over-arching interpretation of these studies is complicated by the small cohorts and the use of various techniques to measure arterial stiffness. It does suggest however, that a vascular wall bereft of molecular reserves for use in enhancement of endothelial function or with pathological remodeling (i.e. vascular smooth muscle hypertrophy) is less vaso-responsive to exercise than vessels with lower basal levels of oxidative stress. Aging and CVD are associated with chronic oxidative stress and inflammation. Ongoing research delineating the molecular pathways leading to mitochondrial deficiencies in energy metabolism and modulation of oxidative stress include assessing the effect of type, intensity, frequency and duration of exercise as well as individual's characteristics with the goal of development of individualized exercise programs [66].

Much of the individual subject data on the salutary biologic effects of exercise comes from modest size clinical investigations during which well-defined groups of patients were typically subject to several weeks of structured exercise. Generalizability and scalability of these studies, particularly to those with existing cardiovascular disease is best accomplished by Cardiac Rehabilitation. This is a well standardized multidisciplinary and multicomponent intervention that is centered on typically thrice weekly supervised exercise sessions and accompanied by a variety of patient educational efforts and psychosocial programming. This general approach to exercise therapy is utilized throughout the world, and has been shown to both safe and effective. Benefits have included documented improvements in a variety of biomarkers that correlate favorably with the atherosclerotic process, and more importantly, positively impact important clinical outcomes, including overall mortality. These demonstrable benefits, accomplished at very low risk of adverse events, have resulted in Cardiac Rehabilitation being recommended by many US and European authorities as an important part of the therapeutic regimen to a wide variety of patients with atherosclerotic disease including: angina, myocardial infarction, and coronary revascularization by either percutaneous coronary intervention or coronary artery bypass grafting. Regimens similar to Cardiac Rehabilitation have been endorsed as useful for patients with other manifestations of atherosclerotic disease including PAD and stroke. There are multiple barriers to individual patients participating in these programs including geographic availability, cost, and endorsement by patients' personal physicians. Cognizance of these potential barriers and their minimization by stakeholders has been repeatedly recommended. Modifications of standard cardiac rehabilitation, including a variety of telehealth methodologies are currently being studied.

Theory applied to practice

Irrespective of the exercise program, the benefits of cardiovascular exercise across the continuum of cardiovascular health makes increasing the physical activity habits of patients (both those who are sedentary and), and those who have already developed clinical manifestations of cardiac disease, a clinical duty every health provider should fulfill.

Practically, although many physicians appreciate the benefits of exercise for the primary and secondary prevention of cardiovascular disease, effective translation of this belief requires more than simply telling patients to "exercise" or "exercise several days a week". The physical activity (PA) National Guidelines call for a minimum of 150 minutes per week of moderate aerobic PA or 75 minutes per week of vigorous aerobic PA; the Institute of Medicine suggests 60 minutes daily of some aerobic PA [67]. If physicians, physical therapists, dietitians and other health professionals all consistently assess and promote PA, as a routine component of every relevant clinical encounter, it is likely that changes in patient physical activity would occur. There is evidence that the more often a provider discusses PA with their patient, the more likely that person is to both recall such advice and to engage in regular PA. Several large health care systems have integrated a PA or exercise vital sign (EVS) into their electronic health record. [67] Patients are asked at every outpatient visit three simple questions relating to the number of days per week, the number of minutes and the intensity of the physical activity. This will foster goal setting and the monitoring of progress towards these goals. Importantly, proper implementation of exercise

guidelines in clinical practice requires that exercise be prescribed for patients in a manner analogous to a drug prescription. Physicians regularly prescribed drugs by enumerating the drug name, the dosage, the dosage frequency, and the timing of administration. Exercise can and should be prescribed similarly, with enough detail to allow the patient, either alone or with the aid of non-physician staff (e.g. cardiac rehabilitation), to engage in an exercise regimen that has been proven to be both safe and beneficial. A useful framework for exercise prescription is the acronym FITT: Frequency, Intensity, Time, and Type (Table 1). For example, a patient may be prescribed an every other day (frequency), moderate intensity (intensity judged by heart rate or perceived intensity), workload such as treadmill inclination and speed, 20 minute (time) walking (type) regimen. Similarly, a patient may be prescribed strength training twice weekly (frequency) 5-pound (intensity) 12 repetition (time) dumbbell biceps curl (type). Including specific details in recommendations and instructions when prescribing exercise for patients will enhance the likelihood of their engaging in safe and effective exercise monitoring and augmentation [68].

Educating health care provider on exercise prescription should be complemented by proper screening of patients during inpatient or outpatient encounters, identifying the populations that benefit from cardiac rehab referrals and making sure the regular barriers to participation in the monitored exercise program are addressed upfront (distance of CR center from home/work, work schedule).

Future Directions

There is compelling evidence of exercise training in general and cardiac rehabilitation in particular. We anticipate future work to further elucidate the biochemical and molecular mechanisms which can help optimize the types and intensities of exercise which will foster personalized regimens in accord with individual's comorbidities, capacity, and goals (i.e. Personal exercise). We believe future clinical trials should evaluate the role of Cardiac Rehabilitation and other structured exercise programs in specific patient populations. To minimize gaps between research and clinical practice, it is key that investigators have clear and complete reporting of the interventions being studied, so that they can ultimately be accurately and effectively implemented by health care providers.[69, 70]

Conclusion

It has been our goal to summarize and explicate the extensive literature supporting the benefits of exercise on atherosclerosis. Though exercise, particularly if done in a manner that produces severe myocardial ischemia may occasionally be detrimental, it is important to understand that there are biologic effects of exercise that favorably influence vascular structure and function, including in the setting of established atherosclerosis. Exercise may be useful as a tool to better understand biologic pathways in health and disease, and favorably modify the overall health of individuals and populations. Indeed, Exercise is Medicine.

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Table 1

Simplified FITT table

	Cardio Exercise	Strength Exercise
Frequency	Five days/week – Moderate intensity [*] Three days/week – High Intensity ^{**} P.S. Increase to six or seven days if aiming at weight loss	Two to three non-consecutive days/week
Intensity	Exercise in target heart rate ^{***} Focus on variety of intensities	Determined by the amount of weight lifted and the reps and sets Goal of 8–10 exercises, around 1–3 sets of 8–16 reps of each exercise
Time	30 to 60 minutes/session - Shorter if exercise is high intensity	Depends on strength and schedule: up to one hour for total body workout, less for split routine workout
Type	Any activity that increases heart rate: running, walking, cycling, dancing...	Activities using resistance: bands, dumbbells, machines, bodyweight exercise

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^{*} Moderate Intensity: 50–69% of target heart rate

^{**} High Intensity: 70-less than 90% of target heart rate

^{***} Target heart rate: The estimated target heart rates for different ages is approximately 50–85% of maximum heart rate. Maximum heart rate used to be estimated at about 220 minus the age, although a more accurate formula used is $206.9 - (0.67 \times \text{age})$ [9, 67].