Abstract: Epidemiologic studies have consistently identified a strong inverse association between coronary heart disease (CHD) and regular, predominantly moderate-intensity physical activity and cardiorespiratory fitness. Supporting evidence of causative relationships has been provided by aerobic exercise training studies in both animals and humans. This research demonstrated multiple plausible cardioprotective biological mechanisms. These include direct antiatherosclerotic effects by improving artery endothelial function and reducing inflammation and indirectly via modification of other risk factor components of the metabolic syndrome, by reducing risk of a coronary thrombotic occlusion (antithrombotic effects), by decreasing myocardial oxygen demands and increasing its vascular supply (anti-ischemic effects), and by improving cardiomyocyte electrical stability and autonomic nervous system adaptations (antiarrhythmic effects).

Despite a progressive decline in rate over the past 5 or so decades, coronary heart disease (CHD) remains the leading cause of death in the United States, as well as a major contributor to disability, lost productivity, and medical expenses. The underlying cause of CHD is atherosclerosis. This chronic inflammatory disorder begins during childhood. It is initiated by multiple risk factors, which cause dysfunction or injury to artery endothelial linings. This results in a cascade of pathophysiological events, including lipid infiltration, primarily of low-density lipoprotein (LDL), and its subsequent oxidation. This triggers a progressive inflammatory response, resulting in formation of fibrocalcific plaques, causing progressive coronary stenosis. However, acute coronary events commonly are triggered by reological disruption of less advanced lesions, characterized by a thin fibrous cap over a large, eccentrically located lipid core and inflammatory cell infiltration (a so-called vulnerable plaque). Plaque disruption initiates platelet aggregation and thrombus formation at the damage site, causing coronary occlusion, which results in myocardial ischemic damage and/or a fatal ventricular tachyarrhythmia.

As is true with most chronic disease processes, atherosclerosis and resulting CHD (as well as a strokes and peripheral artery disease) have a multifactional etiology. Risk factors include nonmodifiable biological factors (genetics, aging, and gender differences) and modifiable physiologic and metabolic factors (especially atherogenic dyslipidemia, hypertension, and diabetes mellitus) and modifiable lifestyle-related/behavioral factors (especially smoking, dietary habits, physical inactivity and associated reduced physical fitness, and overweight/obesity). Physical inactivity is the most prevalent of these modifiable risk factors in the United States, with about two-thirds of Americans performing little or no discretionary physical activity (PA) for recreation or job-related PA. This low level of energy expenditure, along with an associated relative excess in energy intake, has resulted in a high and growing prevalence of obesity and its severity in both American adults and children. Obesity, particularly if it is associated with excess visceral adiposity (as evidenced by increased abdominal girth), is a major independent risk factor for the metabolic syndrome, cardiovascular disease, type 2 diabetes mellitus, and several forms of cancer.

Keywords: exercise; physical activity; physical fitness; atherosclerosis; coronary heart disease

Biological Mechanisms for the Cardioprotective Effects of Aerobic Exercise

Arthur S. Leon, MD, MS
Differentiation is needed between transient effects of each acute exercise session and true chronic adaptations to training.

The inverse association of PA with risk of CHD has been demonstrated in both men and women in the 5 or so decades by an extensive body of epidemiologic observational studies. Meta-analyses of the better quality studies show that the risk of CHD as well as all-cause mortality is about twice as likely in physically inactive as in more active individuals. In addition, a smaller number of studies have reported an even stronger inverse association between cardiorespiratory fitness, as assessed by graded exercise testing, and risk of CHD and all-cause mortality. In these studies, there was more than a 5-fold difference in CHD rate between the least fit and most fit members of the cohorts. Furthermore, it appears from these 2 study approaches that the largest reduction in relative risk of CHD occurs in going from an inactive to a moderately active lifestyle and from a low to a moderate level of physical fitness.

Strong supporting evidence for the postulated partial protective effect of PA and physical fitness against CHD has been provided by experimental work in animals and humans. This research has identified multiple plausible biological mechanisms supporting these relationships. These mechanisms include anatomic, physiologic, and metabolic adaptations to aerobic exercise training. Supporting evidence for these adaptations was recently reviewed in depth in this journal and only will be briefly summarized here. The reader is referred to a more detailed article by Leon and Brona for references to the findings discussed below.

These biological mechanisms may be classified under the following headings: antithrombotic, anti-ischemic, and antiarrhythmic effects.

Antiatherosclerotic Effects

Both morphological assessments of coronary arteries in animals (including monkeys) and atherosclerosis-promoting diets and imaging assessments of human coronary arteries confirm that aerobic exercise training can reduce the progression or contribute to the partial regression of atherosclerotic lesions. Multiple mechanisms appear to contribute to antatherosclerotic effects of exercise. Exercise training, by causing recurrent increases in laminar shear stress on artery endothelium, improves nitric oxide (NO) synthesis and prolongs its activity. The resulting improvement in endothelial function increases vasodilatation and helps protect the coronaries against both atherosclerosis and thrombosis. There also is growing evidence that exercise training increases circulating endothelial progenitor cells, which participate in repair and regeneration of damaged endothelium. Furthermore, exercise training reduces circulating biomarkers of inflammation, including C-reactive protein (CRP), a risk factor related to severity of atherosclerosis.

In addition, exercise training may have a favorable impact on a number of major atherogenic risk factors. These include a reduction in elevated levels of systolic and diastolic blood pressure and favorable impacts on dyslipidemia, insulin sensitivity, and glucose disposal. Furthermore, a concomitant, even moderate, reduction in excess body fat, particularly visceral fat, potentiates the improvement in all of the above risk factors, which are components of the proatherogenic, prodiabetic metabolic syndrome.

Antithrombotic Effects

As mentioned, the vast majority of acute coronary syndromes are initiated by a thrombus-induced coronary occlusion. Improved endothelial function, induced by exercise training, reduces platelet aggregation and a number of blood-coagulating factors, including fibrinogen, and it promotes fibrinolysis by increasing activity of endothelial plasminogen activator.

Anti-Ischemic Effects

Myocardial ischemia is induced by an imbalance between myocardial oxygen (MVO2) demands and its supply via the coronary circulation. An exercise training-induced improvement in maximal oxygen uptake (VO2 max) has a favorable impact on both sides of the MVO2 demand-supply equation. MVO2 demands are reduced at rest and during submaximal physical exertion by a reduction in heart rate and systolic blood pressure (and hence the so-called rate-pressure product). In addition, it reduces MVO2 demands by improving efficiency and capacity of the heart as a pump, as well as by peripheral adaptations in skeletal muscle.

Aerobic exercise training also has been shown to improve MVO2 supply by several mechanisms. These include extending the diastolic period of peak coronary flow by slowing the heart rate and by improving endothelial-induced vasodilatation of coronary resistance vessels by increasing NO synthesis and activity. In addition, moderate-intensity aerobic exercise improves arterial compliance/elasticity, thereby reducing aging-related arterial stiffness. Furthermore, exercise training can increase the luminal area of conduit arteries by remodeling (angiogenesis). In addition, animal studies have demonstrated exercise-induced increases in myocardial capillary density, analogous to the angiogenesis demonstrated in skeletal muscle in both animals and humans.

Antiarrhythmic Effects

Lethal ventricular tachyarrhythmias, often the initial presenting symptom of CHD, are responsible for about two-thirds...
of CHD-related deaths among Americans older than age 35 years. Vigorous physical exertion (>6 metabolic equivalent [MET] intensities) transiently increases risk of sudden cardiac death (SCD), as compared to risk at rest or during more moderate PA. Possible mechanisms for exertion-induced SCD include increased MVO₂ demands in the presence of coronary stenosis, increased sympathetic activity, coronary spasm, or disruption of a vulnerable plaque. However, excess risk of SCD during vigorous PA is markedly lower in those who exercise regularly. This most likely is related to the reduced rate-pressure product and MVO₂ demands and/or its improved supply; direct cardiomyocyte adaptations, improving electrical stability of the heart; and reduced sympathetic and increased vagal stimulation of the heart. These latter training effects can be demonstrated by increased heart rate variability and a decrease in the sympathetic component of the heart rate–blood pressure baroreceptor response to stimuli following exercise training.

**Conclusion**

Much additional research is required to confirm and further elucidate these apparent cardioprotective effects of exercise and to identify possible additional mechanisms. Differentiation is needed between transient effects of each acute exercise session and true chronic adaptations to training. In addition, there is a need to better define the optimal dose-response relationship for producing and maintaining specific exercise-induced adaptations. There also is evidence of considerable interindividual variability in responsiveness to the same training prescription, as demonstrated in the HERITAGE Family Study.

Based on a considerable body of knowledge, reduced risk of CHD can be obtained by the current public health recommendation of 30 to 60 minutes a day on most days of the week of either continuous or intermittent moderate-intensity PA, such as brisk walking. However, to obtain the full gamut of cardioprotective effects of exercise, it appears from the currently available evidence that a formal, more rigorous aerobic exercise training program to significantly increase VO₂ max appears to be required (eg, 20 to 60 minutes at least 3 times per week at 60% to 90% of VO₂ max).

**Acknowledgments**

Appreciation is expressed to Ms Linda Estrem for preparation of this manuscript. No conflict of interest was declared by the author. This material was presented at the 3rd Annual Building Healthy Lifestyles Conference sponsored by Arizona State University in Mesa, Arizona (February 28 to March 1, 2008). The conference was supported by the National Heart, Lung, and Blood Institute (NIH-NHLBI: 1R13HL091657-01). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health; National Heart, Lung, and Blood Institute; or Arizona State University.

**References**