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## Mechanism of beneficial effects of physical activity on atherosclerosis and coronary heart disease

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THE WORLD HEALTH ORGANIZATION ([18](#)) reports that since 1990, more people have died worldwide from cardiovascular disease (CVD) than any other cause. The Centers for Disease Control (CDC; [20](#)) recently reported that a combination of poor diet and physical inactivity was the second leading “actual cause of death” in 2000, causing 16.6% of deaths in the United States. It is widely recognized that the development of atherosclerosis and coronary heart disease (CHD) is blunted by a lifestyle incorporating moderate levels of physical activity ([7](#), [10](#), [22](#), [28](#), [33](#)). The DHHS 2008 Physical Activity Guidelines for Americans (34a) concluded that ... “recently published studies continue to support a strong inverse relation between the amount of habitual physical activity performed and CHD and CVD morbidity or mortality. For both men and women at middle age or older, remaining sedentary is a major

independent risk factor, with persons reporting moderate amounts of activity having a 20% lower risk and those reporting activity of higher amounts or intensity having approximately a 30% lower risk than least active persons.” To put this benefit in proper perspective, this risk reduction equals or exceeds that for statins (5, 19, 36). However, while statin use nearly doubled from 2000 to 2005 to 29.7 million people (30), objective measures of physical activity demonstrate that <5% of the general population meets minimal recommendations for physical activity (34) and patients with CHD are less likely to meet physical activity recommendations than non-CHD individuals (35). Thus the proven efficacy of physical activity in reducing CHD is being largely ignored. Furthermore, the trends are worsening. Comparing the actual causes of death in 1990 and 2000, Mokdad et al. (20) concluded that the most striking finding of their study “ ... was the substantial increase in the number of estimated deaths attributable to poor diet and physical inactivity.”

The cost of physical inactivity in lives, quality of life, and economic loss is profound. In 2000, the health care cost of physical inactivity in California alone was over \$13 billion (6a) and \$86–186 billion nationwide. These findings demonstrate an urgent need to establish a more preventive orientation in health care and public health systems in the United States. The efficacy of habitual exercise in prevention of CHD has been established by prospective, cohort studies in humans demonstrating moderate to high levels of physical activity reduce both morbidity and mortality of CHD (29, 33). Furthermore, meta-analysis of exercise in secondary prevention trials demonstrates a reduction in mortality (33), with some showing regression of existing lesions (25). The potential impact of increasing physical activity on CHD-associated health care is astounding. Hambrecht et al. (13) demonstrated that a combined therapy of exercise and diet was superior to percutaneous coronary intervention (PCI) in event free survival in patients

with stable CHD. In addition, lifestyle modification including exercise cost \$3,500 less per patient, compared with PCI (13). In 2006, more than 1.3 million PCIs were performed in the United States (1), thus optimizing exercise as an alternative therapy to PCI for stable CHD (~60% of all CHD patients) could save over \$2.6 billion annually in health care costs. Obviously, population-wide lifestyle modification could save substantially more.

Using increased physical activity as a preventative measure, both primary and secondary, is also advantageous over therapies targeting isolated lesions. Acute coronary syndromes (ACS) and sudden death are most often associated with rupture of complex, vulnerable plaques that are otherwise clinically benign, i.e., <70% luminal stenosis (6), and not treated clinically by PCI. Furthermore, many patients with unstable CHD have multiple vulnerable plaques. Thus systemic therapies, such as exercise, which simultaneously treat all existing lesions rather than focal strategies that treat only one target lesion, such as PCI, can be argued as superior (6). As concluded by Peter Libby (17), “The concept of ‘interventional cardiology’ should expand beyond mechanical revascularization to encompass preventive interventions that forestall future events.”

Thus while both NIH and the American Heart Association consider inactivity to be an independent risk factor for the development of atherosclerosis and CHD and report that increased physical activity (exercise) is beneficial in prevention and treatment of CHD (8, 22a), the primary mechanisms that underlie the effectiveness of exercise in preventing and/or treating CHD have not been completely established (33). The independence of physical inactivity as a risk factor for CHD (8) is supported by meta-analysis demonstrating that only ~35% of the beneficial effect of exercise on CHD can be attributed to

favorable changes in known risk factors, such as lipid, cholesterol, hypertension, etc. (21). Thus ~65% of the established beneficial effect of exercise on CHD outcomes is unknown. A long established tenet of medicine is that determination of mechanisms provides a compelling scientific basis for prevention and treatment of disease, i.e., evidence-based medicine, while simultaneously opening new avenues for optimal treatment and novel therapeutic development. Thus defining the underlying mechanisms of the beneficial effect of exercise on atherosclerosis and CHD should be a high priority. The beneficial effects of physical activity, independent of changes in risk factors, imply direct effects of exercise on the vascular wall. As summarized by Thijssen et al. (32), “exercise-induced improvements in vessel wall function and structure represent a ‘vascular conditioning’ effect, which provides a plausible mechanistic explanation for the cardioprotective benefits of exercise, independent of the impact of exercise on traditional CV risk factors.” Equally plausible is the contribution of nonvascular adaptations, such as improved ischemic tolerance of the myocardium and or reduced thrombogenicity, emphasizing the necessity of a more global approach to the question of improved CHD outcome by physical activity.

Critical analysis of the literature supports several potential mechanisms for the decreased morbidity and mortality of CHD in habitually active individuals; some of the most compelling are listed in [Table 1](#).

1) Improved endothelial function
2) Attenuated plaque progression/regression and outward remodeling
3) Stabilization of vulnerable plaques preventing plaque rupture
4) Infarct sparing due to myocardial preconditioning
5) Correction of autonomic imbalance

[See full table](#)

**Table 1.** Plausible mechanisms for exercise/coronary heart disease protection

This review series will provide a state-of-the-field perspective on the majority of these mechanisms while additionally providing insight into genetic determinants and translation into disease. The dominant perception that endothelial dysfunction is a “conditio sine qua non for atherogenesis” (11) provides the foundation for perhaps the major postulated mechanism of vascular protection, i.e., endothelial adaptations to exercise. Newcomer et al. (24) explore the role of exercise-induced hemodynamics as it impacts on endothelial and smooth muscle interactions. Along these lines, the potential for enhanced endothelial function and repair by exercise-induced increases in circulating endothelial progenitor cell (EPC) populations is examined by Lenk and colleagues (16). While the role of the endothelium in initiation of atherosclerosis is widely accepted, smooth muscle, particularly intimal smooth muscle, plays a role in both the initiation and progression of atherosclerotic lesions (26, 27) and, importantly, dictates the critical progression to either stable or vulnerable plaque (23). The role and underlying mechanisms of smooth muscle adaptations to exercise as it relates to CHD is examined by Michael Sturek (31) particularly in the context of metabolic syndrome and diabetes. The relatively small impact of chronic exercise on coronary lesion size noted in clinical studies to date compared with the robust effect on CHD incidence and outcome has prompted many to look beyond the vascular wall for the exercise protective effect. This series follows suit by examining the role of training-induced collateralization, alterations in thrombogenicity and “exercise preconditioning” of the myocardium. Drs. Heaps and Parker (14) review the substantial literature regarding the effects of exercise on collaterals and cellular mechanisms underlying adaptation of both the endothelium and smooth muscle of collateral-dependent arterioles. As thrombogenesis is a major component of acute coronary syndromes (ACS) and acute myocardial infarction (AMI), the

effects of acute and chronic exercise on thrombogenicity are examined by Kumar et al. (15).

Although physical inactivity is a powerful modifiable risk factor for CHD, the multifactorial etiology of CHD and the contribution of nonmodifiable risk factors, e.g., genetics, will predict that instances of CHD will develop in even habitually active populations. Importantly, the most prevalent finding from both primary and secondary prevention trials in humans is that exercise reduces mortality and increases survivability after an acute coronary syndrome (29, 33). The ability of prior exercise to impart a cardioprotective effect by limiting infarct size and preserving contractile function following ischemia and reperfusion could account, wholly or in part, for increased survivability following AMI in active individuals. Frasier et al. (9) will critically examine the literature relating to exercise-induced cardiac preconditioning.

Finally, the heterogeneity in response to exercise training among individuals can potentially impact the ability of physical activity to reduce CVD risk. The role of genetic variation on the ability to modify risk factors by exercise will be explored by James Hagberg (12).

While these reviews provide key insights into what is currently known about the relationship between physical activity and atherosclerosis, these reviews also indirectly reveal the equally important questions about what is not known. The reviews identify many such questions in the articles themselves. Some broader, important questions remaining follow.

What are the singular and interactive effects of exercise and lifestyle modification (i.e., diet) on CVD?

Is substantial weight loss required for beneficial effects of exercise?

What is the optimal exercise prescription (frequency, intensity, duration) for CVD reduction? Is the prescription universal or must it be customized?

What nonmodifiable factors (e.g., genetics, age, sex) dictate an individual response to exercise training? Do these influence the optimal dose of exercise for CVD reduction?

Can exercise prevent the progression to complex coronary artery lesions?

Can exercise prevent development of vulnerable plaques?

We hope that the manuscripts submitted in response to this Highlighted Topic series will provide new information addressing these important questions and provide the impetus for future studies. It appears that the field is on the verge of a major advance in understanding how exercise training programs work with lifestyle interventions to prevent and treat CHD.

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## DISCLOSURES

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## **Table 1.**

Plausible mechanisms for exercise/coronary heart disease protection

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- 1) Improved endothelial function
- 2) Attenuated plaque progression/regression and outward remodeling
- 3) Stabilization of vulnerable plaques preventing plaque rupture
- 4) Infarct sparing due to myocardial preconditioning
- 5) Correction of autonomic imbalance
- 6) Reduction in myocardial oxygen demand
- 7) Decreased thrombosis
- 8) Enhanced collateralization
- 9) Decreased inflammatory mediator release from skeletal muscle and adipose tissue

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