President's Council on Physical Fitness and Sports
Research Digest
Series 6, No. 4 Dec. 2005

PHYSICAL ACTIVITY AND NONTRADITIONAL CHD RISK FACTORS:
New Pathways for Primordial Prevention of Coronary Heart Disease

Abstract

Coronary heart disease (CHD) has gained recognition as being preventable through primary or secondary interventions. Scientific advancements over the years have led to a better understanding of the pathogenesis and clinical manifestations of this disease process, and as a result, have led to the identification of a host of traditional and nontraditional factors for use in CHD risk assessment. In addition to traditional and nontraditional factors associated with increased risk, the cardiovascular benefits of physical activity (PA) have been well established and extend well beyond relationships with these conventional CHD risk factors. In recent years, substantial data from observational cohort and exercise training studies, as well as from randomized controlled trials, support that the existence of cardioprotective effects of PA or planned exercise may be mediated by several nontraditional CHD risk predictors. These include markers of inflammation and thrombosis, autonomic nervous system (ANS) regulation, and endothelial function. The purpose of this review is to discuss the epidemiological and experimental evidence for the role that PA has in modifying these new, up-and-coming clinical determinants of CHD risk. The frequency, duration, and intensity of exercise used in these studies generally are consistent with the consensus recommendations for cardiovascular benefits in apparently healthy and clinical populations. Available data are not clear as to whether PA-related improvements in these emerging risk predictors represent a different pathway for prevention of clinical CHD events. Future research studies should examine whether different PA-related pathways for cardiovascular health exist and define the impact that PA and planned exercise has on these pathways.

Published quarterly by the
President's Council on
Physical Fitness and Sports
Washington, D.C.

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Introduction

Coronary heart disease (CHD) has a lengthy incubation period during which biological risk factors interact with genetic and environmental influences to initiate and promote atherosclerotic plaque development, endothelial cell dysfunction, and arterial stenosis. Eventually these events precipitate clinical manifestations of angina, myocardial infarction, and sudden death.[1,2] Current CHD prevention is based on a "high-risk" framework wherein risk factor thresholds guide the initiation and intensity of clinical interventions.[3] Advancements in the clinical management of biological risk factors have afforded considerable progress in the prevention of initial (*primary prevention*) and recurrent (*secondary prevention*) clinical CHD events.[4] *Primordial prevention* is a less often used term and refers to modifying the *primal* or *earliest* contributors of disease occurrence (Figure 1).[4,5] Only a small proportion of individuals will express clinical CHD because of genetic predisposition.[6] For most individuals the principal determinant is their lifestyle.[7,8] Thus, primordial prevention of CHD requires elimination of the environmental and lifestyle origins of atherosclerotic risk factors rather than simply treating risk factors that have exceeded a clinical threshold.[5] In this regard, physical activity (PA) has been recognized as a central element in primordial CHD prevention.[4]

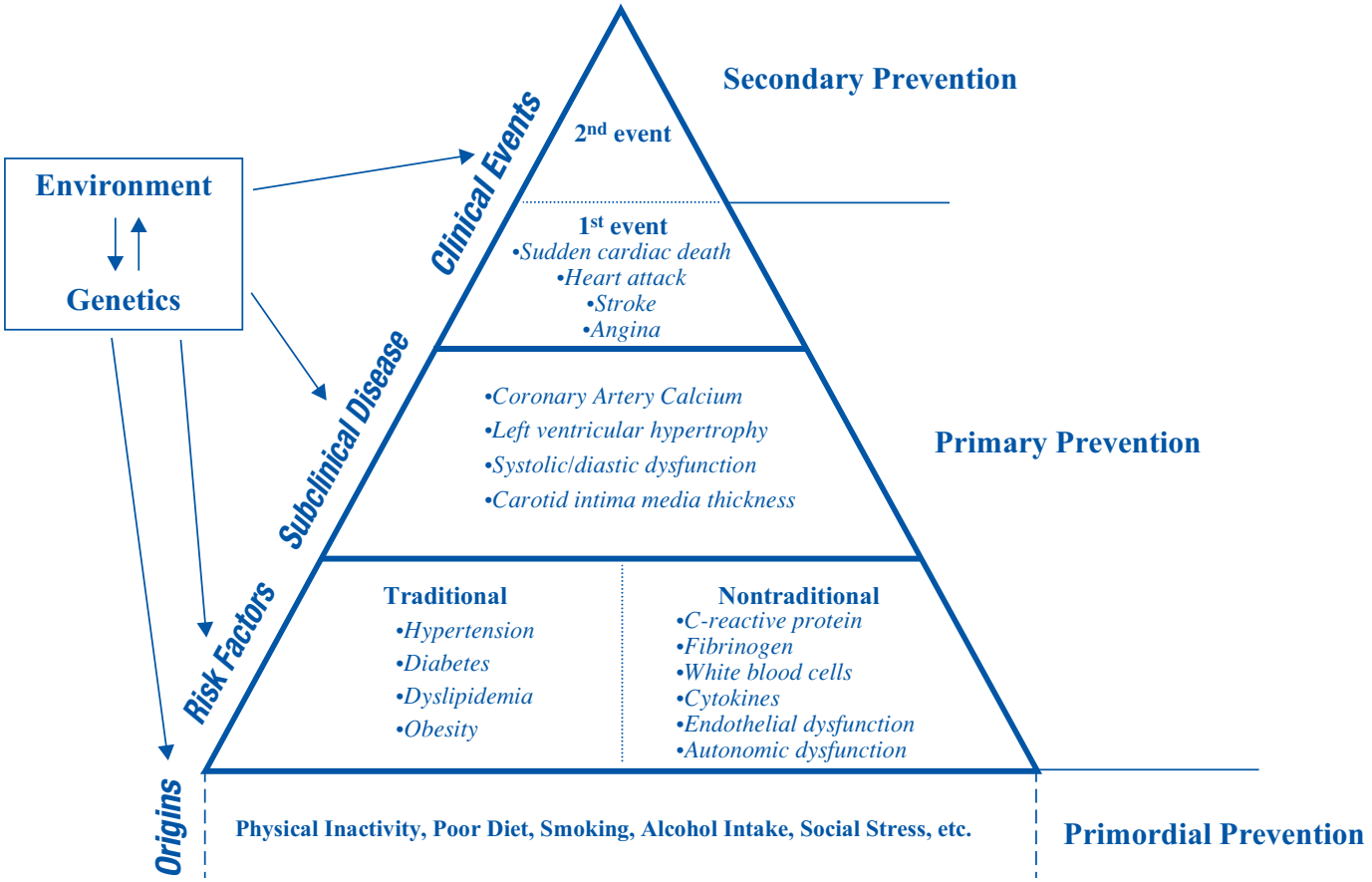

Figure 1

Higher levels of PA are associated with favorable CHD risk factor profiles.[9] Observational studies support an inverse dose-response association between PA and CHD events that is independent of traditional CHD risk factors (e.g., smoking, hypertension, dyslipidemia, etc).[10] Recent advancements in understanding the pathogenesis of CHD have identified a host of new potential CHD risk predictors.[2,11] Whether these nontraditional risk markers are intermediate in the causal pathway between PA and CHD is not well understood, but there may be additional pathways through which PA exerts primordial CHD prevention.

Two previous papers in the *Research Digest* focused on the cardioprotective aspects of PA. Haskell broadly reviewed the quality and strength of existing evidence supporting physical activity for primary and secondary CHD prevention,[12] and more recently, Bassuk and Manson provided a review on physical activity and cardiovascular disease prevention in women.[13] Here, we will expand on these previous works by discussing epidemiological and experimental evidence of the role that physical activity has in modifying new and emerging clinical determinants of CHD risk. In order to achieve this objective our focus is specifically on three aspects of atherogenesis for which the influence of PA has recently been evaluated: (1) inflammation and thrombosis, (2) autonomic nervous system dysfunction, and (3) endothelial dysfunction and vascular conductivity.

Inflammation and Thrombosis

Inflammation plays a key role in the initiation, progression and thrombotic manifestations of CHD.[2,14] Observational studies on apparently healthy cohorts of women and men show that several inflammatory markers, including C-reactive protein (CRP), fibrinogen, white-blood cell count (WBC), and numerous cytokines (e.g., IL-1, IL-6, TNF-alpha), are associated with increased risk of CHD events, and are independent of most CHD risk factors.[15]

The relationship of inflammatory markers with self-reported PA levels or measures of cardiorespiratory

fitness (CRF) has recently been examined in large observational cohorts. Significant inverse associations with PA and CRF are reported for CRP, fibrinogen and WBC in middle-aged[16-19] and older[20,21] individuals. These associations generally have a dose-response gradient and are independent of age, sex, race, medication usage, and CHD risk factors including smoking and body mass index (BMI). Hormone replacement therapy also is associated with higher levels of CRP in women.[22] However, available data suggest that the inverse relationship between CRP and PA or CRF is independent of hormone replacement therapy.[23-25] Most studies adequately address issues pertaining to acute illness, smoking, and exercise at the time of the baseline blood collection, use appropriate statistical methods for the typically skewed distribution of CRP, and exclude excessively high CRP concentrations (e.g., >10 mg/L) from the analysis.

Although cross-sectional data suggest an anti-inflammatory effect of regular PA, such analyses are not sufficient for establishing causal relationships. Observational data on changes in PA and related changes in inflammatory markers provide more convincing evidence of cause and effect. A recent 20-year follow-up study of 3,810 British men 40-59 years old indicated that changes in reported leisure-time PA were associated with changes in CRP, fibrinogen, and WBC.[21] Most importantly, men who reported increased activity had significantly lower levels of each inflammatory marker than men who reported sustained physical inactivity or whose PA decreased during follow-up.

Experimental evidence is required to definitively determine whether increased levels of PA result in lower markers of subclinical inflammation. Several recent studies addressed this issue. Lakka et al.[26] reported changes in CRP concentrations in 652 initially sedentary women and men (mean age 35.6±13.7 years; 33% African American) following 20 weeks of aerobic exercise training at 55-75% of $\dot{V}O_{2max}$ for 90-150 minutes per week. A 24% reduction in CRP concentration (P<0.001) was seen in participants with initial CRP levels >3.0 mg/L, independent of sex, race, and changes in most traditional CHD risk factors including plasma insulin and body weight. There were no exercise-related changes in CRP in participants with baseline CRP≤3.0 mg/L. In another study of 63 women and men 50-75 years of age, 24 weeks of aerobic exercise training at 50-70% of $\dot{V}O_{2max}$ for 60-120 minutes per week resulted in a 15% reduction in mean CRP concentrations. These reductions were independent of biological factors and three selected CRP genotypes.[27] A study of 199 Japanese women (mean age 52±10 years; 54% postmenopausal) who completed 8 weeks of moderate intensity aerobic exercise training for 110-140 minutes per week had reductions of 35% and 8% in mean CRP and WBC, respectively (P<0.001 each). These changes were independent of changes in insulin sensitivity and weight loss.[28] Exercise training also has been related to reductions in inflammatory markers in patients with clinically manifest CHD. Milani et al.[29] reported a 41% reduction in the median CRP concentration (P<0.01) in 235 patients (mean age 67±11 years; 29% women) following 3 months of Phase II rehabilitation that included 3 days per week of aerobic exercise at 70-85% peak heart rate. Reductions in plasma CRP remained significant even when patients were grouped on lipid-lowering drug use and weight loss characteristics.

Reductions in CRP following exercise training provide compelling evidence of an anti-inflammatory effect from regular moderate intensity PA. However, the above-reported studies were not randomized controlled trials, thus caution is required when interpreting and generalizing the reported findings. The US Diabetes Prevention Program recently reported 1-year changes in CRP and fibrinogen in 3,234 adults with impaired glucose tolerance following randomization to a lifestyle intervention (physical activity, diet modification, weight loss), metformin (an insulin-sensitizing drug), or a control group.[30] A 2% reduction in mean fibrinogen concentrations was seen in the lifestyle group (P<0.01 with placebo and metformin groups). CRP was reduced by 30% in the lifestyle group (P<0.001 with placebo and metformin groups), though partial correlations suggested that weight loss was more influential in lowering CRP than was increased physical activity.

Autonomic nervous system dysfunction

Through its parasympathetic and sympathetic divisions, the autonomic nervous system (ANS) supplies both afferent and efferent nerves to the heart and circulatory system. Thus, the ANS is a major component in cardiovascular regulation. Defects in many reflex control mechanisms are often associated with manifest signs of CHD such as increased peripheral vascular resistance, reduced cardiac parasympathetic control, altered baroreceptor function, and reduced sympathetic activity in response to variety of stimuli.[31-34] Clinical assessment of ANS function is difficult, and as a result, ANS parameters have not been routinely used in individual CHD risk assessment.

Analysis of heart rate variability (HRV) is accomplished by using the electrocardiogram (ECG). Because the ECG reflects both sympathetic and parasympathetic function, it is the most common measure of cardiovascular autonomic function. Other noninvasive methods of assessing ANS function include determination of baroreflex sensitivity and heart rate recovery after termination of exercise.

Lower HRV is associated with an increased risk of cardiac events and mortality in apparently healthy individuals and in CHD patients.[35-41] In the Atherosclerosis Risk in Communities Study (ARIC), 2-minute beat-to-beat HRV assessed with a resting ECG was inversely associated with the risk of developing CHD.[37] Individuals in the lowest category of HRV had a 72% ($P<0.05$) higher risk of incident CHD compared with the upper 75th percentile of the HRV distribution independent of age, sex, race, education, medication use and CHD risk factors. However, the relatively short period of HRV data collection used in ARIC[36,37] and other studies,[40] provides only a limited assessment of sympathetic activity. In the Framingham Heart Study, HRV was assessed from 2-hour ambulatory ECG recordings in 1,101 men and 1,400 women who were free of CHD at baseline.[35] During a mean follow-up period of 3.5 years, a 1 standard deviation decrement in HRV was associated with a 47% ($P<0.05$) increased risk of new cardiac events.[35] Depressed parasympathetic activity was positively associated with the development of arrhythmia and cardiac events in CHD patients[42,43] and apparently healthy individuals.[35,38,40]

Few cross-sectional studies have examined the association between PA and the autonomic nervous system. In general, available data indicate that physically active individuals have significantly higher HRV than their sedentary peers.[44,45] In a large observational study of British Civil Servants,[45] total leisure-time PA and both moderate- and vigorous-intensity activity were associated with higher HRV in men. The association occurred in a dose-response gradient independent of age, and was observed across strata of BMI. Consistent with other findings,[46,47] HRV was not associated with PA in women in this study.

Other investigators evaluated the association between HRV and CRF by using objective measures such as recent PA habits and cardiac functional reserve.[48-50] De Meersman[48] observed higher CRF and HRV in 72 male runners (aged 15 to 83 years) compared to 72 age- and weight-matched sedentary control subjects. Furthermore, Davy et al.[50] showed that age contributes to a decline in HRV in women independent of CRF levels. However, women with higher CRF had higher HRV at any age compared with their sedentary peers. Carnethon et al.[51] evaluated the relationship between habitual physical activity levels and heart rate change during recovery from a maximal exercise tolerance test. Post-exercise recovery heart rate was used as a measure of cardiac vagal reactivation, and thus, a surrogate of ANS function (e.g., faster recovery heart rate reflects better vagal reactivation and better ANS function) among 3,446 women and men from the Coronary Artery Risk Development in Young Adults (CARDIA) study.[51] In women and men, higher levels of self-reported PA was associated with faster post-exercise heart rate decline, independent of age, sex, race, BMI, and other CHD risk factors. Furthermore, maximal exercise testing repeated at 7 years post-baseline showed that participants who reported decreased PA during the 7-year follow-up had significantly slower heart rate recovery than did participants who reported maintaining or increasing their PA.

Although cross-sectional reports suggest that regular PA is associated with better autonomic function, data from exercise training studies demonstrate conflicting results. A meta-analysis by Sandercock et al.[52] examined whether aerobic exercise interventions in healthy subjects is associated with increases in HRV. The overall finding was a small but significant correlation between HRV and aerobic exercise training, which supports the current theory that aerobic exercise training favorably alters the cardiac neuroregulatory control in healthy women and men. Investigations included in this meta-analysis had small sample sizes and lacked control groups, but still found trends towards enhanced HRV that were not statistically significant.

Studies in apparently healthy adults provide support for substantial benefits in parasympathetic autonomic control that occurs within the first 2-4 months of moderate intensity aerobic exercise training.[53-55] Recently, 88 sedentary overweight postmenopausal women with elevated blood pressure were randomly assigned to a control group or 2 months of moderate intensity (50% $\dot{V}O_{2max}$) aerobic exercise training for an average of 141 minutes per week.[53] Women in the exercise group experienced a 25% increase in HRV ($P<0.01$) that was independent of reductions in resting heart rate, whereas women in the control group had a 5% decrease in HRV. More prolonged and intense

exercise training does not appear to systematically enhance these adaptations.[54,56] The largest randomized controlled trial to examine the effect of aerobic exercise on HRV was conducted in 140 Finnish men (age 57±3 years) who exercised 5 times per week at 40-60% at $\dot{V}O_{2max}$ for 45-60 minutes per session over a 5-year intervention period.[57] Despite a mean increase of 11% in submaximal CRF at 12 months among men in the intervention group, exercise training had no effect on HRV or at a subsequent 5-year evaluation. However, exercise compliance was low (~39%).

Regular physical activity as a part of a comprehensive rehabilitation program has also been shown to produce beneficial effects on autonomic function in CHD patients.[58-60] Iellamo et al.[60] showed that short-term intense exercise training after myocardial revascularization significantly increased CRF, baroreflex sensitivity and HRV. Blumenthal et al.[61] randomized CHD patients into a 16-week aerobic exercise training intervention and observed a significant improvement in baroreflex sensitivity compared with usual care controls. This finding is important because abnormal baroreflex sensitivity is associated with poorer prognosis in patients who recently had a myocardial infarction.[43] Thus, exercise training might be an effective nonpharmacological tool to enhance autonomic cardiac control in CHD patients.

The biological mechanisms through which exercise enhances autonomic cardiovascular control are poorly understood. Important functional cardiac adaptations to prolonged endurance exercise training include improved diastolic function and increased stroke volume. These changes, together with small decreases in afterload resulting from peripheral adaptations to endurance exercise, enhance the volume work and lower the pressure work completed by the heart. This change in the type of cardiac work completed in turn lowers myocardial metabolic demand and results in a lower heart rate and enhanced HRV at a given external work rate. Endurance exercise training also contributes to lower circulating catecholamine levels, which may improve autonomic regulation by enhancing parasympathetic cardiovascular control. Future consideration should be given to whether ANS parasympathetic function may also be enhanced by the effect that regular PA has on conventional CHD risk factors such as glucose and insulin levels, lipid profiles, and arterial blood pressure. Studies are needed to more fully elucidate the specific mechanisms that underlie the associations between PA, ANS function and CHD risk.

Endothelial dysfunction and vascular conductivity

One of the earliest manifestations of atherogenesis is endothelial dysfunction, preceding angiographic or ultrasonic evidence of atherosclerotic plaque.[62] Many investigators have shown that coronary endothelial dysfunction is associated with increased CHD risk.[63-65] Because the healthy endothelium serves as a "gatekeeper" regulating substances moving in and out of the arterial wall, the preservation of endothelial function is a major goal in the prevention and management of CHD.

Direct assessment of endothelial function can enhance the identification of asymptomatic individuals who are at high risk for CHD events. However, the invasive nature of these techniques limit their routine use in clinical practice.[11] The most common indirect method of assessing endothelial dysfunction uses high-resolution ultrasound to measure brachial artery diameter in response to reactive hyperemia, a transient increase in local blood flow following a brief arterial occlusion.[66] The increased blood flow and resulting shear stress on the arterial wall stimulates the release of nitric oxide, a potent vasodilator and important chemical messenger for normal endothelial regulatory functions. Referred to as flow-mediated vasodilation (FMD), this phenomenon is a marker of endothelial-dependent vascular reactivity and is inversely associated with adverse CHD risk factor profiles.[67]

Physically active individuals tend to demonstrate better endothelial function compared with their sedentary peers. Rinder et al.[68] reported greater FMD in older male athletes (mean age = 68±2 years) whose $\dot{V}O_{2max}$ was 42 ml/kg/min as compared with age-matched sedentary men whose $\dot{V}O_{2max}$ was 27 ml/kg/min. These findings suggest that prolonged participation in physical activities and preservation of CRF may attenuate age-related declines in endothelial function. Exercise training in asymptomatic individuals with normal endothelial function produces relatively little or no added benefit on endothelial function. The majority of studies undertaken in subjects with impaired endothelial function, however, have shown improvements in the endothelial function of conductance vessels. Hambrecht et al.[69] reported that 4 weeks of supervised cycle ergometry exercise at 80% of peak heart rate in CHD patients (mean age 60±2 years) was associated with a significant

improvement in coronary artery endothelial responsiveness to acetylcholine administration measured invasively by Doppler. Hambrecht et al.[70] also recently reported on 101 men with stable CHD who were randomized to 1 year of aerobic exercise training at 70% peak heart rate or to percutaneous revascularization. Significantly higher 1 year event-free survival was seen in the men who exercised compared with those who underwent revascularization (88% versus 70%, P=0.02). Both groups experienced significantly improved myocardial perfusion, however, cardiovascular functional capacity (e.g., $\dot{V}O_{2max}$) increased only in the exercise group.[70] These studies underscore the importance of exercise training for improving coronary flow reserve and myocardial perfusion in CHD patients.

Exercise training also improves endothelial function in the peripheral arterial system. Hambrecht et al.[71] found that 6 months of moderate intensity (70% $\dot{V}O_{2max}$) aerobic exercise training for 20 minutes per day was associated with a 20% reduction in total peripheral resistance versus 6% increase in the control group. The exercise training improvement in peripheral resistance was also accompanied by improved skeletal endothelial function.

The consistency of the published data indicates that exercise training improves endothelial function in individuals with existing vascular disease, independent of conventional CHD risk factors. Impaired FMD secondary to depressed bioactivity of nitric oxide may respond to exercise training in as little as 4 weeks, however, sustained physical inactivity rapidly reverse this process.[72]

Summary

Primary and secondary CHD prevention is currently employed in a high-risk setting where risk factor thresholds guide the initiation and intensity of intervention. Because the burden of CHD is large, advancements in our understanding of the pathogenesis and clinical expression of CHD have led to the identification of a host of traditional and nontraditional factors for use in CHD risk assessment. The cardiovascular benefits of physical activity are well established and extend beyond relationships with conventional CHD risk factors. Considerable data from observational cohort and exercise training studies as well as a limited amount of data from randomized controlled trials suggest that the cardioprotective effects of PA or planned exercise may be mediated by several nontraditional CHD risk predictors such as markers of inflammation and thrombosis, ANS regulation, and endothelial function. The frequency, duration, and intensity of exercise used in these studies generally was consistent with the consensus recommendation for cardiovascular benefits in apparently healthy and clinical populations.[73] However, few studies have quantified the physical activity data as caloric expenditure. The lack of complete exercise caloric quantification information makes comparisons and contrasts for reported findings in the literature difficult. Considerably more research is needed using diverse samples of women and men to determine the dose-response characteristics between PA and each of the risk factors discussed in this review. Whether PA-related improvements in these risk predictors represent another pathway for primordial prevention of clinical CHD events remains to be seen, and should be considered in future research on PA and cardiovascular health.

The consistency of the published data indicates that exercise training improves endothelial function in individuals with existing vascular disease, independent of conventional CHD risk factors.

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