The Association Between Physical Activity and the Development of Acute Coronary Syndromes in Treated and Untreated Hypertensive Subjects

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The objective of this study was to evaluate the effect of physical activity on the risk of coronary events in different groups of hypertensive patients. During 2000–2001, 848 patients hospitalized for a first event of coronary heart disease and 1078 hospitalized controls without any suspicion of coronary heart disease, paired by sex and age, were randomly selected from all Greek regions. A total of 418 (49%) of the patients and 303 (28%) of the controls were classified as hypertensives, while 88 (21%) of the hypertensive patients and 88 (29%) of the hypertensive controls, reported regular leisure-time physical activity. Compared to physical inactivity, the analysis showed that light to moderate physical activity was associated with a reduction by 12% of the coronary risk in controlled hypertensive subjects (p=0.03), by 9% (p=0.04) in hypertensives who were untreated or unaware of their condition, and by 5% (p=0.087) in uncontrolled hypertensives. The practice of regular physical activity seems to be associated with lower coronary risk in various groups of hypertensives. However, these data cannot prove causality, and prospective studies will be necessary to confirm or refute the authors' findings. (J Clin Hypertens. 2003;5:115–120)

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Throughout the 20th century the level of blood pressure has been recognized as a determinant of the risk for several common cardiovascular diseases, including coronary heart disease, cerebrovascular disease, and heart failure.[1–5] Data from the World Health Organization[3] show that the number of hypertensives, worldwide, is estimated to be 600 million people. Of them, 3 million will die as a result of hypertension. It is also estimated that only one half of the hypertensive patients worldwide are aware of their condition, and that only one half of those are treated. Furthermore, only one half of the treated hypertensives achieve optimal blood pressure levels. Thus, only 12.5% overall are adequately controlled. Recent data from Greece[6] suggest that almost one fourth of adults have hypertension. There is evidence to support the idea that several factors related to lifestyle habits may influence blood pressure levels.[4,5] Among them, the beneficial effect of physical activity on human health has been underlined in several studies. It is generally accepted that moderate exercise can significantly reduce the levels of blood pressure in patients with mild to moderate essential hypertension, and consequently reduce the coronary risk.[4,6–10]

The aim of this work is to evaluate the association between leisure-time physical activity and the risk of developing a first acute coronary syndrome (ACS) event, in various groups of hypertensive

subjects. In particular, we focused our attention on subgroups of subjects who were treated and controlled, untreated or unaware of their condition, and treated but uncontrolled.

METHODS

The CARDIO2000 is a multicenter retrospective case-control study[6] investigating the association between several demographic, nutritional, lifestyle, and medical risk factors with the risk of developing a first event of nonfatal ACS. Data collection took place between January 2000 and August 2001. The sample size was decided through power analysis, in order to evaluate differences in the coronary relative risk greater than 7% (statistical power >0.80; significance level <0.05). According to the population distribution provided by the National Statistical Services (Ministry of Economics, census 2000), we stratified our sampling into all the Greek regions, in order to include various socioeconomic levels and cultural particularities of the investigated population. Data on risk factors were collected through validated questionnaires, and physical and clinical measurements.

Study Population

During the aforementioned period 1926 randomly selected patients and controls entered the study. Of these, 848 were patients (695 males, 58±10 and 153 females, 65±9 years old) who entered the hospital for a first acute coronary event. The inclusion criteria for cardiac patients (cases) were: 1) first event of acute myocardial infarction diagnosed by two or more of the following features: typical electrocardiographic changes, compatible clinical symptoms, or specific diagnostic enzyme elevations, according to the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) classification[11]; or 2) first diagnosed unstable angina corresponding to class III of the Braunwald classification.[11]

Following selection of the cardiac patients, we randomly selected 1078 subjects (830 males, 58.8±10 years old and 248 females, 64.8±10 years old) without any clinical symptoms or suspicions of cardiovascular disease in their medical history (controls), matched to the patients by age (±3 years), sex, and region. Controls were mainly subjects who visited the outpatients department of the same hospital and during the same period as the coronary patients, for routine examinations or minor surgical operations. In a few cases (in county hospitals), where the available number of hospitalized controls was not sufficient for the matching procedure, we enrolled into the study friends or colleagues of the coronary patients. We used these types of controls in order to have more accurate medical information, to eliminate the potential adverse effect of unknown confounders, and to increase the likelihood that cases and controls shared the same demographics. The information regarding the investigated medical factors was obtained from the subjects' medical records. A specialist obtained the information regarding the lifestyle characteristics through a confidential questionnaire during a specific interview.

Exposure Parameters

Physical activity was defined as any type of nonoccupational physical exercise practiced at least once per week, during the past year. It was graded in qualitative terms such as light (expended calories <4 Kcal/min, e.g., walking slowly, stationary cycling, light stretching, etc.); moderate (expended calories 4–7 Kcal/min, e.g., walking briskly, cycling outdoors, swimming with moderate effort, etc.); and vigorous (expended calories >7 Kcal/min, e.g., walking briskly uphill, long distance running, cycling fast or racing, swimming a fast crawl, etc.) as done by Pate et al.[12] The rest of the subjects were defined as physically inactive. Any subject with comorbidities that might affect physical activity status was excluded from this analysis. The evaluation of nutritional habits was based on a validated questionnaire following the guidelines from the Department of Nutrition of the National School of Public Health.[13,14] In keeping with the long-standing classification criteria used in several population-based studies,[15,16] patients who reported never having been told of having hypertension, who were not currently taking any antihypertensive medication, and whose blood pressure was less than 140/90 mm Hg were classified as normotensives. Patients whose blood pressure was ≥140/90 mm Hg, or who were taking antihypertensive medication, were classified as hypertensives. Hypertensive patients were then asked the following question: "Have you ever been told you have hypertension?" Those who answered "No" to the question were classified as "Unaware Hypertension." Those who answered, "Yes" but were not currently taking antihypertensive medication were classified as "Untreated Hypertension." Patients who were treated, but their blood pressure was not controlled (>140/90 mm Hg) were classified "Uncontrolled Hypertension." Finally, the rest of them were assigned to the group of "Controlled Hypertension."

According to the collected medical records, the majority of the controls (78%) and of the patients (72%) had at least one blood test during the past 12 months. In order to cover the lack of medical

information we also measured total cholesterol and blood glucose levels during the first 12 hours of hospitalization. Based on the collected information, hypercholesterolemia was defined as cholesterol levels greater than 220 mg/dL, or greater than 200mg/dL, when two other risk factors for coronary heart disease were present or the patients were on cholesterol-lowering treatment. Diabetic subjects were those with fasting blood glucose greater than 125 mg/dL, or those who were on hypoglycemic treatment. In addition, obesity was defined as a body mass index >29.9 kg/m^2; current smokers were defined as those who smoked at least one cigarette per day (quantification of smoking status was based on the calculation of pack-years adjusted for nicotine content equal to 0.8-mg per cigarette); and alcohol consumption was measured by daily ethanol intake, in glasses (100 cc, 12% ethanol). Educational level was classified into three groups on the basis of self-administered questionnaires: group I, up to high school; group II, high school but not college; and group III, college. The mean annual income during the past 5 years was also recorded. Regarding the other investigated parameters, the aims and the design of CARDIO2000 have already been presented.[6,14]

Statistical Analysis

Continuous variables are presented as means±one standard deviation, while qualitative variables are presented as absolute and relative frequencies (%). In order to fit multivariate risk models an exploratory analysis was initially applied. Stratified contingency tables with calculation of chi-squared test, Student *t* test, and analysis of variance, were used to evaluate differences between the continuous variables and the outcome. Estimations of the relative risks of developing ACS according to physical activity and hypertension status (the main factors of interest), were performed by the calculation of odds ratio (OR) and the corresponding confidence intervals through multiple, conditional, logistic regression analysis. The effect of physical activity by hypertension status was tested by evaluating the interaction terms {physical activity: none, light, moderate, and vigorous} × {hypertension level: normotensive, hypertensive–controlled, and hypertensive–uncontrolled} in the multivariate model. The significance of the previous interaction term as well as the potential confounding effect of body mass index, smoking habits, alcohol consumption, educational and financial status, and the presence of diabetes mellitus, hypercholesterolemia, or any special medication associated with the outcome of ACS, was tested through stepwise methods. In particular, the final model was developed through backward elimination procedures for the selection of variables, based on the Wald's statistic and using 5% of the probability for including and 10% of the probability for excluding a variable from the model. Finally, deviance residuals were calculated in order to evaluate the model's goodness-of-fit. All reported *p* values are from two-sided tests and compared to a significant level of 5%. STATA 6 software (STATA Corp., College Station, TX) was used for the calculations.

RESULTS

Description of the Sample

Four hundred and eighteen (49%) of the patients and 303 (28%) of the controls (ages 62±10 vs. 63±9 years, respectively; p=0.353) were defined as hypertensives. These were classified as (numbers and percentages of patients, and controls): controlled hypertensives (155, 19%; 122, 12%), acknowledged but untreated hypertensives (94, 11%; 34, 3%), treated but uncontrolled (148, 17%; 111, 10%), and unaware of their condition (21, 2%; 36, 3%). The statistical analysis showed significant differences between coronary patients and controls by hypertension status (p<0.001). Eighty-eight (22%) of the hypertensive patients and 88 (29%) of the hypertensive controls reported some physical activity (p=0.078). The rest of them were defined as physically inactive. Table I demonstrates the characteristics of the hypertensive patients and controls according to the reported physical activity status. No associations were found between physical activity status and the prevalence of several cardiovascular risk factors or other demographic characteristics among patients and controls.

In comparison to subjects who reported a sedentary lifestyle, those who were physically active were of younger age (59±10 vs. 61±10 years old; p<0.001), and they were more likely to adopt a "healthy dietary pattern" (rich in fruits, vegetables, legumes, fish, and olive oil) (26% vs. 21%; p=0.087). All the previous relationships as well as those reported in Table I were considered potential confounders in the subsequent analysis.

The Effect of Physical Activity on Coronary Risk in the Different Hypertensive Groups

In order to test the hypothesis: "whether physical activity levels are associated with the risk of developing ACS, in various groups of hypertensives," we applied multivariate analysis, controlling for the effect of several potential confounders that might

Table I. Characteristics of Hypertensive Patients and Controls, by Physical Activity Status

	PATIENTS (N=418)		CONTROLS (N=303)		*P* VALUE
Physical activity	Yes	No	Yes	No	
Number (%)	88 (22%)	330 (78%)	88 (29%)	215 (71%)	0.08
Male/Female	72/16	257/73	72/16	161/54	0.25
Hypercholesterolemia	54 (61%)	211 (64%)	36 (41%)	95 (44%)	0.41
Current smoking	55 (62%)	211 (64%)	39 (44%)	97 (45%)	0.40
Diabetes mellitus	31 (35%)	102 (31%)	17 (19%)	39 (18%)	0.35
Obesity	18 (20%)	86 (26%)	21 (24%)	62 (29%)	0.38
Family history of CHD	34 (39%)	162 (49%)	14 (16%)	47 (22%)	0.07
Income (#.000 US$)	17.2±2.9	15.8±2.6	18.1±3.7	15.2±2.3	0.48
Education					0.04
Group I	75 (85%)	166 (50%)	46 (52%)	106 (49%)	
Group II	27 (31%)	53 (16%)	27 (31%)	25 (12%)	
Group III	25 (28%)	28 (8%)	23 (23%)	16 (7%)	

CHD=coronary heart disease

influence the main outcome of interest, i.e., prevalence of ACS in hypertensives. The results, after taking into account the effect of age, gender, presence of hypercholesterolemia, diabetes mellitus, smoking habit, body mass index, premature history of coronary heart disease, medication, education, and nutritional habits, showed that any level of regular physical activity, compared to sedentary life, was associated with a significant reduction of the coronary risk in controlled hypertensives (Table II). For example, light physical activity, compared to sedentary life, was associated with a 12% (OR, 0.88) lower coronary risk in controlled hypertensives. Moreover, a similar benefit from physical activity on the risk of development of ACS, seemed to exist in the other groups of hypertensives, too (Table II). Finally, the adoption of a physically active lifestyle was associated with a 31% (OR, 0.69; 95% confidence interval 0.54–0.89) lower risk of developing ACS in normotensives.

DISCUSSION

In this work we aimed to evaluate the effect of physical activity levels on the risk of developing ACS, in various subgroups of hypertensive subjects. After controlling for several potential confounders, we observed that the adoption of a low to moderate physically-active lifestyle was significantly associated with the reduction of the risk of developing ACS. This finding seems to hold not only in controlled hypertensives, but also in patients who were uncontrolled, untreated, or unaware of their condition.

Several studies have shown that the risk of coronary heart disease mortality or morbidity is inversely related to the level of physical activity.[7,8,12,17–19] The protective role of physical activity on cardiovascular morbidity has been attributed to the favorable effects of physical exercise on the traditional coronary risk factors. However, the level of physical activity for a beneficial impact on coronary risk factors remains controversial. The Centers for Disease Control and Prevention, and the American College of Sports Medicine recommend at least 30 minutes of moderate-intensity physical activity on most, preferably all, days of the week on the basis of documented improvements in fitness.[17] This level of activity is well tolerated by most middle-aged or older individuals. Moderate-intensity exercise is also more effective in lowering blood pressure than high-intensity exercise in patients with mild to moderate essential hypertension.[19] It is also well tolerated by patients with severe hypertension and, when combined with antihypertensive medication, is more efficacious in lowering blood pressure than medication alone.[20] Thus, the evidence suggests that even severe hypertension can be managed with a combination of drug therapy and physical exercise.[18–21] However, the mechanisms responsible for the underlying exercise-induced reduction in blood pressure levels remain unclear.[11]

Table II. Results From the Multivariate Analysis (OR; 95% CI) for the Evaluation of the Effect of Physical Activity on the Risk of Developing ACS in Several Groups of Hypertension

	Odds Ratio	95% CI
Physical activity status in controlled hypertensives		
None (reference category)	1.00	
Light	0.88	0.77–0.99
Moderate	0.87	0.76–0.98
Vigorous	0.85	0.75–0.96
Physical activity status in unaware or untreated hypertensives		
None (reference category)	1.00	
Light	0.95	0.78–1.16
Moderate	0.87	0.75–0.98
Vigorous	0.85	0.78–0.92
Physical activity status in acknowledged, uncontrolled hypertensives		
None (reference category)	1.00	
Light	0.98	0.82–1.31
Moderate	0.93	0.79–1.08
Vigorous	0.87	0.78–0.96

Variables entered in the model: age, sex, and region (by design), presence of hypercholesterolemia, diabetes mellitus, smoking (in pack-years), family history of coronary heart disease (CHD), medication related to CHD, nutritional habits, education and financial level
OR=odds ratio; CI=confidence interval; ACS=acute coronary syndromes

Our study showed that the adoption of even low to moderate physical activity levels, by controlled hypertensives, seems to be associated with a reduction of coronary heart disease risk, after taking into account the effect of the cardiovascular risk factors as well as other potential confounders (Table II). Although there is a trend in the reduction of the relative risk by the physical activity levels (Table II), it seems that the effect of vigorous physical exercise did not significantly alter the previous finding. This is in accordance with other studies that showed that mild to moderate intensity exercise can be more effective in lowering blood pressure levels than higher-intensity exercise.[22] Furthermore, several investigators believe that moderate-exercise intensity is better tolerated by patients, and carries a relatively lower risk for cardiac complications.[23] Finally, and encouraging from a public health perspective, is the finding that the inverse association seems to exist, even in the subgroups of hypertensives who are untreated or unaware of their condition as well as in the treated but uncontrolled patients. However, the mechanisms by which physical activity reduce the coronary risk were not evaluated in the present study. It could be the possible moderation of several other unmeasured factors or the effect of several unknown confounders. Thus, prospective studies measuring incidence will be necessary to clarify questions of risk and etiology.

This study reveals the important role of the adoption of a physically active lifestyle by various groups of hypertensive subjects in the primary prevention of coronary heart disease. Although the design of case-controlled studies does not allow us to evaluate evidences for causality, this assumption can be a strong key message for public health purposes. Consequently, public health policy makers should focus their efforts on informing the community about the crucial importance of healthy lifestyle conditions that impede the development of acute coronary events.

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