ORIGINAL RESEARCH

Physical Inactivity is Related to Unheralded Myocardial Infarction More Than Uncomplicated Stable Angina

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ABSTRACT

Background: Ischemic heart disease can vary substantially in its clinical presentation. Some patients have acute myocardial infarction (MI) without any previous signs of myocardial ischemia, whereas other patients may have stable angina pectoris for years without periods of acute instability; this suggests the possibility of different risk influence in these 2 groups of patients.
Methods: Cardiovascular risk factors were compared in 112 consecutive patients with unheralded MIs (81 men; 59.9 ± 11.6 years) and in 168 consecutive patients with chronic stable angina (108 men; 58.2 ± 10.5 years) with at least 60% occlusion in lumen diameter in 1 of the coronary vessels.
Results: Logistic-regression analysis revealed that physical inactivity (odds ratio [OR]: 4.32, 95% CI = 2.07, 8.99; $P < 0.0001$), the values of high sensitive-C-reactive protein levels (OR: 1.05, 95% CI = 1.00, 1.11; $P = 0.043$), diabetes (OR: 2.88, 95% CI = 1.42, 5.83; $P = 0.003$), and positive family history of premature coronary artery disease (OR: 1.96, 95% CI: 1.04, 3.71; $P = 0.038$) were independent predictors of unheralded MI versus chronic stable angina.
Conclusion: In our subjects, sedentary life, diabetes mellitus, positive family history of premature coronary artery disease, and higher high sensitive-C-reactive protein levels were important independent predictors for unheralded MI, which suggests that these factors are involved in thrombosis, plaque rupture, or both. *Journal of Clinical Exercise Physiology*. 2018;7(3):46–52.

Keywords: angina pectoris, myocardial infarction, atherosclerosis, C-reactive protein

INTRODUCTION

During past decades, some studies have debated whether the acute and chronic manifestations of ischemic heart disease occur as a chance on a common atherogenic substrate, while others suggest patients are more vulnerable to one of these presentations as a result of specific risk factors or genetic determinants. Severe coronary atherosclerosis may exist for years without causing an acute coronary event. However, the initial presentation of ischemic heart disease may be myocardial infarction (MI) without previous angina pectoris (1,2). This difference in the clinical picture has been confirmed with angiographic studies that report a more extensive atherosclerotic burden in patients with chronic stable angina pectoris (CSA) than those with

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acute MI (1,2). Angiographically, minimal coronary lesions may be associated with acute progression, severe or total occlusion, and may account for the majority of patients who will suffer acute coronary syndromes (ACSs) in the future (1,2). These differences between patients with stable angina pectoris and MI have led to an assumption of a pathogenetic dichotomy between acute and chronic presentations of coronary artery disease (CAD) and between thrombogenesis and atherogenesis (3–7).

Physical activity affects many metabolic and other pathways that influence cardiovascular risk factors. Physically inactive people often have other behaviors associated with an increased risk for cardiovascular disease (CVD), such as obesity, smoking, and unhealthy diet (8), but improvement of individual risk factors with physical activity is often modest, in spite of large reductions in CVD risk seen with physical activity (8).

We therefore sought to investigate the effects of physical activity on inflammatory and metabolic indices in subjects at the end of the clinical spectrum of ischemic heart disease: those with an unheralded MI compared to those with chronic stable angina.

MATERIALS AND METHODS

A cross-sectional, case-control study was carried out on 112 patients with acute MI and 168 patients with CSA who were treated at the Tehran Heart Center. Myocardial infarction was confirmed if symptoms met World Health Organization criteria (9).

Subjects with CSA were selected from consecutive patients undergoing elective coronary angiography and were defined as having at least 50% occlusion in lumen diameter in one or more coronary vessels. Patients also had no history suggestive of unstable angina or MI, and the electrocardiography, echocardiography, radionuclide, or contrast ventriculography results were not suggestive of an old MI. Subjects with clinically significant renal, hepatic, hematologic, or systemic disease, suggesting the existence of other diseases that may influence inflammation such as peripheral arterial disease, and those taking steroid/immunosuppressive drugs for recent trauma were also considered ineligible to participate in the study. Those with a history of cancer, unless in clinical remission or considered cured for at least 5 years, were also excluded, and patients with ongoing or recent (<1 month) inflammatory or infectious diseases were excluded. The study was approved by the ethics committee of the hospital and was conducted in conformity with Helsinki Declarations. Informed consent was obtained from all patients before the study commencement.

Data was collected for participants and recorded on data sheets for the following: demographic data including sex, age, health behaviors, including smoking, physical activity, and personal and family history of diabetes and hypertension, as well as the history of any kinds of treatment modalities of diabetes and hypertension.

An active smoker was defined as a person who had smoked at least one cigarette per day for ≥6 months. Passive smokers were defined as patients who reported having been exposed to passive smoke at home and/or at work at least 1 hour per day for at least 1 year (10).

Physical activity level was estimated by a questionnaire developed by an expert panel at our institution. The questionnaire contained items assessing the minimum, maximum, and average amount of time (number of hours and days) spent each week during the previous year engaging in moderate physical activity (e.g., brisk walking requiring 3.5 or more metabolic equivalents of task per hour) and vigorous physical activity (e.g., strenuous sports and jogging that required 7 or more metabolic equivalents of tasks per hour) at each time point. Individuals with at least 150 minutes of moderate-intensity aerobic physical activity or 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity were considered physically active. Patients were allowed to perform their physical activity continuously or in bouts of at least 10 minutes duration (11).

The participants received a complete physical examination including weight and height circumference and blood pressure measurements. Weight (kg) was measured while the patient was dressed in light clothing and without shoes using digital scales and recorded to the nearest 0.5 kg. Height was measured and recorded to the nearest 0.5 cm in a standing position, without shoes, using a stadiometer, with the shoulders in a normal, relaxed position. Body mass index was calculated by dividing weight (kg) by the square of height (m^2).

Blood pressure was measured by standard mercury sphygmomanometer with an appropriate sized cuff for arm diameter. Before measurement, the participant was questioned about drinking tea or coffee, having physical activity, smoking, and full bladder. The participants were required to rest for at least 5 minutes before having their blood pressure checked twice at an interval of at least 5 minutes. The mean value of these 2 measurements was used for the analyses.

Venous blood samples were obtained after at least 10 hours of overnight fasting for the determination of plasma glucose, serum high sensitive-C-reactive protein (hs-CRP), and lipid concentrations. Blood samples were taken according to the standard protocol and were immediately centrifuged. Fasting plasma glucose was measured by enzymatic colorimetric method using glucose oxidase. Serum total cholesterol, triglycerides, and high-density lipoprotein cholesterol were determined by enzymatic methods using commercial kits. Low-density lipoprotein cholesterol was calculated using the formula of Friedewald (12). In case serum triglyceride concentration was greater than 400 $mg \cdot dL^{-1}$, low-density lipoprotein cholesterol was determined directly. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography method (Nyco-Card, Axis-Shield CO., Rodelokka, Oslo, Norway). The hs-CRP test was performed using a solid phase enzyme linked immunosorbent assay (ELISA, Parsazmun, Karaj, Iran).

TABLE 1. Clinical and biochemical characteristics of subjects with angina pectoris without previous known acute coronary event and subjects with acute unheralded myocardial infarction.

	Stable Angina (n = 168)	Myocardial Infarction (n = 112)	P Value
Age (yrs)	59.9 ± 11.7	58.2 ± 10.5	0.22
Male (n, %)	108 (64)	81 (72)	0.16
Body mass index ($kg \cdot m^{-2}$)	26.7 ± 4.4	29.45 ± 22.9	0.21
Systolic blood pressure (mmHg)	97 ± 11	99 ± 14	0.33
Diastolic blood pressure (mmHg)	83 ± 14	81 ± 10	0.069
Total cholesterol ($mmol \cdot L^{-1}$)	5.8 ± 1.5	5.9 ± 4.0	0.892
Low-density lipoprotein cholesterol ($mmol \cdot L^{-1}$)	3.5 ± 1.8	3.3 ± 1.3	0.28
High-density lipoprotein cholesterol ($mmol \cdot L^{-1}$)	1.3 ± 0.3	1.3 ± 0.3	0.86
Triglycerides ($mmol \cdot L^{-1}$)	1.9 ± 1.2	1.5 ± 1.1	0.006
Family history of early MI (n, %)	41 (24.4%)	39 (34.8%)	0.1
Current smoking (n, %)	43 (25.6%)	39 (34.8%)	0.09
Passive smoking (n, %)	23 (13.7%)	45 (40.2%)	<0.001
Diabetes (n, %)	68 (51.1%)	65 (48.9%)	0.005
Hypertension (n, %)	103 (61.3%)	68 (60.7%)	0.1
Hyperlipidemia (n, %)	142 (84.5%)	83 (74.1%)	0.04
Hs-CRP ($mg \cdot L^{-1}$, IQR)	3.27 (1.35–6)	3.78 (1.35–9.4)	0.02
HbA1C (%, IQR)	5.8 (5.2–6.7)	5.95 (5.4–7)	0.09

Abbreviation: MI = myocardial infarction
Data are mean ± standard deviation and median (interquartile range, IQR); or number (percentages, %) where indicated.

Hypertension was defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg or receiving antihypertensive medications. Dyslipidemia was defined as receiving lipid-lowering agents or total serum cholesterol ≥200 $mg \cdot dL^{-1}$ (5.2 $mmol \cdot L^{-1}$), or serum triglyceride ≥200 $mg \cdot dL^{-1}$ (2.3 $mmol \cdot L^{-1}$) (13). Coronary angiography was performed by the femoral approach using standard techniques, and CAD was defined as ≥50% luminal narrowing of at least 1 major epicardial vessel. Diabetes was defined as fasting blood sugar ≥126 $mg \cdot dL^{-1}$ [≥7.0 $mmol \cdot L^{-1}$], HbA1c ≥ 6.5%, or receiving hypoglycemic medications (14).

Statistics

Data were analyzed with SPSS (version16.0; SPSS, Inc., Chicago, Illinois). Central measures of normal dispersion were used: mean ± standard deviation or median (interquartile range) for quantitative variables and percentages in the case of qualitative variables. The differences between the groups were evaluated with the use of the χ^2 test for categorical variables. For continuous variables, 2 independent sample Student's *t* tests were used. The results were reported with unadjusted means, whereas the independent power of the risk factors was evaluated with multiple logistic regression analysis including age, gender, physical activity, hypertension, smoking, diabetes, family history, hyperlipidemia, hsCRP, and HbA1c. All tests were 2 tailed, and probability values were considered significant at the 0.05 level.

RESULTS

The clinical and biochemical characteristics of the patients with chronic stable angina without a preceding acute coronary event and subjects with unheralded MI are shown in Table 1.

Of the 112 subjects with MI, 72.3% were male, and of the 168 subjects with stable angina, 64.3% were male. There was no difference in the sex makeup of the groups. The mean age of the subjects was also not different between the groups.

The groups were also comparable with respect to body mass index, hypertension, and a positive family history of early MI (Table 1). Smoking was more frequent in subjects with unheralded MI than patients with CSA ($P < 0.001$). The mean number of cigarettes used per day was 7.5 in subjects with unheralded MI and 3.9 in the CSA group ($P = 0.002$). Significantly more subjects with CSA had hyperlipidemia ($P = 0.04$), while the MI group was more physically inactive and had a higher incidence of diabetes ($P = 0.002$ and $P = 0.005$, respectively). The total amount of physical activity of the study groups is shown in Table 2.

The comparison of the unadjusted levels of hs-CRP and HbA1c between the 2 groups (Table 1) revealed a significant difference for hs-CRP ($P = 0.02$), but not HbA1c (P = not significant). When the HbA1c comparison was adjusted for age, sex, and hs-CRP, a trend was detected ($P = 0.056$; Table 3). Comparison of HbA1c between groups in nondiabetic patients yielded no significant difference (P = not significant).

TABLE 2. Level of physical activity of subjects with angina pectoris without previous known acute coronary event and subjects with acute unheralded myocardial infarction.

	Males			Females		
	Stable Angina	Myocardial Infarction	P Value	Stable Angina	Myocardial Infarction	P Value
Minutes of physical activity per day						
Minimum	16.0 ± 23.0	9.0 ± 22.1	0.037	6.5 ± 15.4	0.5 ± 2.7	0.004
Maximum	28.9 ± 42.5	16.4 ± 43.2	0.048	10.3 ± 25.1	1.3 ± 7.2	0.011
Average	22.4 ± 32.0	12.7 ± 32.2	0.041	8.4 ± 19.0	0.9 ± 4.9	0.007
Days of physical activity per week						
Minimum	2.3 ± 2.9	0.8 ± 2.0	<0.001	0.9 ± 2.1	0.2 ± 1.3	0.055
Maximum	2.7 ± 3.3	0.8 ± 2.0	<0.001	1.0 ± 2.3	0.2 ± 1.3	0.031
Average	2.5 ± 3.1	0.8 ± 2.0	<0.001	1.0 ± 2.0	0.2 ± 1.3	0.041
Average time of physical activity per week	131.6 ± 193.1	52.9 ± 156.3	0.002	44.0 ± 106.4	6.2 ± 34.6	0.014
Physical inactivity (%)[a]	75.0%	91.4%	0.004	93.3%	100.0%	0.295

[a] Physical inactivity reported as the percent of the total sample that did not achieve at least 150 minutes of moderate-intensity or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity

Data are mean ± standard deviation.

Logistic-regression analysis revealed that physical inactivity (odds ratio [OR]: 4.317, 95% CI = 2.073, 8.988; $P < 0.0001$), the values of hs-CRP levels (OR: 1.053, 95% CI = 1.002, 1.106; $P = 0.043$), diabetes (OR: 2.875, 95% CI = 1.419, 5.825, $P = 0.003$), and positive family history of premature CAD (OR: 1.961, 95% CI = 1.038, 3.706; $P = 0.038$) were independent predictors of unheralded MI versus CSA. Hyperlipidemia (OR: 2.346, 95% CI = 1.301, 4.232, $P = 0.005$) was found to be an independent risk factor for CSA.

DISCUSSION

During the past decade, some studies have tried to answer the question whether the differences in clinical and angiographical presentations are made by different risk profiles in patients with unheralded MI compared with those in patients with CSA. Bogaty et al. (3) investigated a number of atherogenic hemostatic, inflammatory, and genetic variables in highly selected patients at the extremes of the clinical spectrum of ischemic heart disease, but did not find any significant differences for these risk factors in the groups. They concluded that acute coronary events occur randomly in the presence of coronary atherosclerosis rather than in association with a specific biologic risk profile. However, other studies have found a variety of differences in the two categories, but no consistent pattern has emerged (4–6,15). The present study indicates that sedentary lifestyle, diabetes mellitus, positive family history of premature CAD, and higher hs-CRP levels were the most important risk factors for MI.

TABLE 3. Risk of myocardial infarction versus stable angina according to highly sensitive-C-reactive protein (hs-CRP), glycated hemoglobin (HbA1c) and physical activity.

Variable	Adjusted Variables	Odds Ratio	95% CI	P Value
hsCRP	Age, sex, and HbA1c	1.055	1.005, 1.108	0.030
	Age, sex, hypertension, smoking, diabetes, family history, and hyperlipidemia	1.052	1.003, 1.103	0.038
HbA1c	Age, sex, and hsCRP	1.167	0.996, 1.367	0.056
	Age, sex, hypertension, smoking, diabetes, family history, and hyperlipidemia	0.980	0.800, 1.200	0.843
Average time of physical activity per week	Age and sex	0.997	0.995, 0.999	0.001
	Age, sex, and hsCRP	0.997	0.994, 0.999	0.001
	Age, sex, hsCRP, hypertension, smoking, diabetes, family history, and hyperlipidemia	0.996	0.994, 0.998	<0.001

These findings suggest that these factors may be involved in plaque rupture, thrombosis formation, or both. Hyperlipidemia was more prevalent in patients with CSA.

Many epidemiological studies have shown that low physical activity is a strong and independent risk factor for both CVD and all-cause mortality (16,17). Approximately 60–85% of adult populations around the world are not active enough to benefit their health. Unfortunately, this situation is not improving, especially in the rapidly growing cities of the developing world (18). Physical activity acts through many metabolic and other pathways that affect CVD risk factors. Regular physical activity reduces body weight, lowers blood pressure, improves function and cardiorespiratory fitness, lowers the resting heart rate, and modestly improves plasma lipid profile (19,20). Furthermore, physical activity promotes the hemodynamic functioning of the heart. In addition, people who are physically active often have other health behaviors associated with a decreased risk for CVD, such as lower rates of smoking and a higher intake of fruits and vegetables. However, changes in individual risk factors with physical activity seem to be modest, on the order of 5% for blood lipids (21), 3 to 5 mmHg for blood pressure (22), and 1% for hemoglobin A1c, in spite of large reductions (30 to 50%) in CVD risk seen with physical activity (8). Additionally, longitudinal evidence suggests that persons who are more physically active have lower inflammatory markers, most notably CRP (23).

Because physical activity must be regular and continuous to confer protection, the benefits achieved may be partly because of short-term effects, such as effects on blood coagulation, fibrinolysis, and platelet aggregation (24), viscosity (25), or inflammatory indices such as CRP. Our results indicate that physical activity is inversely associated with risk of MI independent of other cardiovascular risk factors. This may be via inflammatory modulation, which is of critical importance in the pathogenesis of CVD (25).

It is known that the incidence of coronary heart disease is increased in patients with diabetes compared with nondiabetics (14). In our study subjects with similar values of HbA1c, diabetes was an important independent predictor of unheralded MI, which suggests that the presence of diabetes, apart from the status of diabetes control and HbA1c value, is involved in the progression of coronary atherosclerosis to MI. This is in contrast with the findings of Bogaty et al. (3) and Dunder et al. (4) that there was no distinction between subjects with MI and CSA. This is also contrary to a study by Gaspardone et al. (6) in which the prevalence of diabetes was higher in patients with CSA.

There are sparse and controversial reports regarding the risk of hyperlipidemia for CSA and MI (26). Serum lipids are an important risk factor for the development of both stable and acute coronary heart disease in several studies (3,4). Gaspardone et al. (6) found that, in patients with otherwise similar coronary risk factors, higher levels of HDL appeared to be associated with a reduced tendency of coronary atherosclerosis to cause ACS. In our study, dyslipidemia and higher serum level of triglycerides were higher in patients with CSA. It is conceivable that a part of the reduced tendency of coronary atherosclerosis resulting in an MI among our patients with CSA is the greater usage of antihyperlipidemia medications, particularly statin-class medications. The mechanism through which statins confer their postulated beneficial effects is uncertain. Statins may have antithrombotic effects unrelated to cholesterol reduction (27) and anti-inflammatory effects through the downregulation of cytokines (28). Statins may also influence the vascular subcellular milieu to shift vasoactive factors toward vasodilation (29). Finally, in experimental models of MI and heart failure, statins normalized the sympathetic outflow and reflex regulation and attenuated the left ventricular remodeling (30).

In our study, although the percentage of smokers in the CSA group compared to the MI group showed a trend, the average number of cigarettes smoked in the MI group was significantly higher than the ACS group. Previous studies showed that smoking was a more important risk factor of initially diagnosed ACS (7). The risk of acute MI increases with the number of cigarettes smoked per day (31).

Inflammation is known to have a role in the progression of atherosclerosis and is considered to be a promoter of the disease. Elevated levels of hs-CRP have prognostic value with respect to cardiovascular events in patients from several different nations (32,33). Whether CRP reflects the inflammatory component of atherosclerotic plaques or of the circulating blood, and whether it is a surrogate marker or a biologically active element in plaque development of thrombus formation at the site of the atherosclerotic vessel is still a matter of debate. It has been recently reported that hs-CRP correlates with the number of vulnerable atherosclerotic plaques prone to rupture (34). These findings suggest that the increased risk of future coronary events observed in patients with elevated serum hs-CRP is related to the increased number of vulnerable plaques (34). However, in the study by Empana et al. (5), higher systemic levels of hs-CRP, interleukin-6, interleukin-18, and intercellular adhesion molecule-1 were equally predictive of stable angina pectoris and ACS. Thus, the possible plaque rupture-triggering effect of inflammation was not specific to unstable disease in this study. Our findings suggest that hs-CRP serum level is increased in patients with ACS and provides support of a role of hs-CRP as a major risk factor for the development of clinical manifestations of CAD.

Although a limitation of our study was the selection of patients who survived their MI, a strength was the stringent clinical characterization of the patients into subsets of acute (MI) and chronic (ACS) CAD groups with meticulously acquired histories, electrocardiography, and left ventricular wall motion studies. The patients of this study were not representative of the majority of CAD sufferers. However, an analysis limited to well-characterized subjects at the extremes of the clinical spectrum of those with CAD may provide different insights compared with a more heterogeneous subject group. An additional limitation was that medications that have a documented anti-inflammatory effect (i.e., statins, angiotensin converting enzyme, nonsteroidal

anti-inflammatory drugs) were not documented and thus not controlled for during statistical analysis. Finally, the use of the recall method to assess physical activity status over a long period of time is an additional limitation based on the potential of inaccurate recall.

CONCLUSIONS

In our subjects, sedentary lifestyle, diabetes mellitus, positive family history of premature CAD, and higher hs-CRP levels were important independent predictors for unheralded MI, which suggests that these factors are involved in thrombosis, plaque rupture, or both. The result of this study may implicate physical activity, quitting smoking (potentially including passive smoking), and prevention of the effects of diabetes as the most favorable targets to stabilize existing atherosclerotic plaques. Because the number of subjects in our study was small, specific recommendations cannot be made. Further studies with larger sample sizes and prospective cohort and interventional studies are recommended to be conducted to confirm proof of this concept.

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